ANNALS of ALLERGY

Published by
The American College of Allergists

Volume 12 | May-June, 1954 | Number 3

PRESIDENTIAL ADDRESS

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New York, New York

IT BECOMES my pleasant assignment to report that The American College of Allergists has successfully realized all the objectives of the new by-laws adopted by the Board of Regents in April, 1953. The Board of Directors, ably chaired by J. Warrick Thomas, has functioned magnificently and efficiently. The executive vice president, Eloi Bauers, conducted the various tasks of this new office with predictable despatch and with maximum results. Ethan Allan Brown has done himself proud as the Editor of ANNALS OF ALLERGY and with Hal McC. Davison as Co-Chairman arranged a commendable postgraduate course in allergy which immediately preceded the Allergy Congress. To Giles Koelsche I owe a personal debt of gratitude for his objective and judicial management as chairman of the Committee on Certification and over-all chairman of the Committee on Scientific Program and Instructional Course. As a consequence of these successful efforts, the work of Fred Wittich, Secretary-Treasurer, though still voluminous and arduous, was carried on more smoothly, to the advantage and best interests of the College. To all the gentlemen mentioned and to the officers and members of the Board of Regents I am grateful and thankful for making it possible to report that during my term as president, the College has successfully weathered uncertain times. I have every confidence and faith in my worthy successor, Dr. Homer Prince, to guide the College to increased importance and eminence in organizational medicine.

ALLERGY PRACTICE TODAY

Now a word about the current trend in allergy practice. There is a need to pay attention to the insidiously creeping paralysis of empiricism in

Presidential Address, Decennial Congress, The American College of Allergists, April 9, 1954, Miami Beach, Florida.

allergy thinking and treatment. This empiricism has been speeded up with the advent of the "Miracle Drugs" which have created the practice of employing the easiest way out of the problem of treatment for the intractable and even average allergy patient. This situation requires correction if we hope to check a slow deterioration of the art and science of the practice of allergy.

From an immunologic and therapeutic viewpoint specific allergenic treatment remains the most reliable and effective method for relieving the large majority of hay fever and asthma sufferers. In recent times the allergist has become aware of the psychological aspects of allergy and is already treating the allergic patient as a total human being rather than a person with merely an allergic disorder.

AMERICAN FOUNDATION FOR ALLERGIC DISEASE

About March, 1953, the American Foundation for Allergic Diseases was incorporated in the State of New York. This foundation is sponsored by both national allergy societies. It is a national, voluntarily supported, nonprofit organization of physicians and laymen for work in the field of allergy. It will ethically present the subject to the public, stimulate research in allergy and the allergic diseases, improve medical training and induce more competent young physicians to specialize in allergy, increase hospital and clinic facilities for allergy patients, develop home care and ambulatory treatment for less-privileged patients and encourage the program for the rehabilitation of the "chronic pulmonary cripple," especially the intractable chronic asthmatic child not responding to modern allergy practice in his own community. The Foundation's program is being guided by an efficient medical public relations organization. The Foundation is the only acceptable link between organized allergy and the public. The initial success of launching the Foundation is the responsibility of the allergists. The allergists for their own protection are obliged to nurse the Foundation during its first year of operation and your voluntary financial support is needed. Your contribution will prove to be a worthwhile investment. The president of the Foundation, Dr. Horace S. Baldwin, is a conscientious, diligent, untiring and intelligent gentleman. He is doing a sound job. Our faith and trust in his leadership are well founded.

TEACHING OF ALLERGY

It is common knowledge that the teaching of allergy in medical schools is haphazard and inadequate. In some medical schools, allergy is neglected entirely. Due to the lack of hospital and clinical services, interns and residents have few opportunities for observation of patients. As a result there is a dearth of well-trained young allergy specialists.

There is a need to encourage the establishment of a separate Department of Allergy in the hospitals of this country. A natural subsequent goal is the establishment of a separate department of allergy in our medi-

cal schools. It is important to request that the patients be properly and humanely treated by competent allergists since allergic diseases rank third in prevalence among chronic diseases in the United States today. At least 10 per cent of the population has some allergic disease and there are at least 4,000,000 asthma and hay fever sufferers. It is therefore, essential for all medical men to recognize allergy diseases early and that their treatment should be kept up to date. This becomes an almost insurmountable task when the medical schools in this country continue to underestimate the needs of an important segment of our ailing population.

Thus, the ever-increasing demands for more and improved care of the allergic population has become the direct responsibility of the allergy specialists. In recognition of this growing need the American College of Allergists has for some years set up an intensive postgraduate instructional course in allergy, for practitioners of medicine. Such a course has just been completed by the College.

ALLERGY CERTIFICATION

Closely related to the problem of undergraduate and postgraduate instruction in allergy is that of certification for allergists as separate and full specialists.

Allergy as a specialty was first challenged in 1939 when allergy became a sub-specialty of the American Board of Internal Medicine. The picture was changed a few years ago when allergy was further fractionated to become a sub-specialty of the American Board of Pediatrics.

Sensing that unity and strength of purpose among allergists were primary requisites to hold the allergists together, the two national allergy societies, represented by a Joint Committee on Certification, have, for six years, unsuccessfully appealed to the Advisory Board for Medical Specialties for a separate American Board of Allergy. These denials pose a serious threat to the future development, if not the survival of allergy as it is practiced today.

However, last September, a separate American Board of Allergy seemed to have emerged from its certification vacuum and hopes for obtaining recognition almost reached the highest realistic peak. One month later (October) the allergists of this country suffered a most unexpected setback, a notorious and painful denial by the American Board of Pediatrics. The failure of the Joint Committee on Certification, chaired by George Piness, to deliver positive results, is an understandably keen disappointment for all of us. This then is the record. Yet, the matter cannot be allowed to rest.

In organizational allergy where the overwhelming forces of allergists are aligned for survival, there is no room for maneuvering in the sidelines or for the hazardous game of neutralism. The choice is between co-operation with the forces of freedom for allergy certification and for the path of slavish subcertification. The American College of Allergists

and the American Academy of Allergy have chosen long ago freedom for allergists. We have committed ourselves to a separate American Board of Allergy within the framework of the Advisory Board of Medical Specialties. We remain committed. United we shall carry on the crusade holding firm to the viewpoint that the allergists of this country are mature enough to be able to see through any plan endangering the establishment of a separate board of allergy.

During this meeting hearings have been held between the Committee on Certification and the Pediatric Allergists and the issues involved have been carefully reviewed and studied. It is gratifying to report satisfactory and constructive progress has been made toward bringing about the wishes of the vast majority of allergists as represented by the College and the Academy.

We feel the hour is getting late. And the allergists of America in unison earnestly hope for a quick and favorable response to their question, "When will this confusion end?"

450 West End Avenue

ZEPHIRAN EASES FEAR OF INJECTION

Dr. Ellen P. MacKenzie writes in the *Journal of Pediatrics* (44:421, April 1954) that the often-hysterical fear of pain from an injection experienced by some children can be eliminated in many cases by temporarily anesthetizing the site with a frozen solution of Zephiran (Winthrop-Stearns). Zephiran is a cationic detergent and germicide of high bactericidal and bacteriostatic potency. It is non-irritating to tissues in proper dilutions. The skin-cooling procedure with Zephiran is effective and simple. A 1:1,000 aqueous solution of Zephiran, with coloring material added for psychological effect, is poured into ordinary ice trays and placed in a refrigerator to freeze. The antiseptic properties of the solution are unchanged by freezing. Prior to injection the area is rubbed with an ice cube until well chilled and "temporarily anesthetized," when the injection is given rapidly with a sharp needle. The psychological reaction to piercing the skin is eliminated, as shown by the relieved laughter of older children who report "it didn't hurt" and return without fear for later injections, Dr. MacKenzie says. The technique was used with all patients old enough to fear injections, involving skin-puncturing procedures that did not require a dry field.

THE USE OF PROTEIN SKIN TESTS IN THE CELIAC SYNDROME

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IN A STUDY of celiac patients, one of us (J.H.E.) has found that the majority are improved by removing gluten from the diet, that the majority can tolerate starch which is free of gluten, but that other foods may also cause disturbance in some of these patients. This confirms the reports of Dicke,[6] Weijers,[13] Anderson[2] and Sheldon.[12]

The diagnosis of celiac disease is reserved for those children who have satisfied the criteria laid down in most modern textbooks of pediatrics—failure to thrive, abnormal undigested stools, enlarged abdomen, and in the majority reduced glucose tolerance and vitamin A absorption. Normal pancreatic enzymes were found in all cases in which a diagnosis of fibrocystic disease of the pancreas had to be considered as the differential diagnosis. The majority of cases were already controlled or reasonably well controlled by dietary means, and were gaining in height and weight.

The purpose of this study was to determine the correlation, if any, between skin test reactions and clinical experience. Convalescent and controlled patients, without signs of the active phase of celiac disease, were tested.

SKIN TESTS

Twenty-eight cases were skin tested with forty-seven of the common foods including wheat, barley, oats, rye and rice and with the wheat protein fractions which were obtainable, namely, gliadin, globulin, glutenin and proteose.* All tests were done by the intracutaneous method with a full realization of the limitations of skin tests with foods, particularly in gastrointestinal allergy. The forty-seven common foods were tested within the following concentrations: fruits, vegetables, meats and cereals except wheat and arrowroot in 1:500 dilution; egg, milk and wheat in 1:5000 dilution followed by a 1:1000 dilution if the weaker test was negative; all other foods in a 1:1000 dilution. These concentrations are the ones used in routine testing in the Allergy Clinic and are considered to be fairly reliable indices of skin sensitivity. On the assumption that the wheat fractions would behave similarly to the wheat antigen the 1:5000 followed by the 1:1000 dilutions were used with these four fractions on the twenty-eight cases. To check the reliability of these tests, similar tests with the wheat fractions were done on twenty-three control patients chosen at random only on the basis that they were of comparable age

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Presented at the Decennial Annual Congress of the American College of Allergists, Miami, Fla., April 9, 1954.

*Kindly supplied by Hollister-Stier Laboratories.

(average four years 1 month, range eight months to eight years and six months) and that they were on a diet containing wheat and evidencing no sensitivity to it. It was found that both the experimental and control cases gave a large number of positive reactions to the wheat fractions with the 1:1000 dilution and therefore these reactions were disregarded and only reactions to the 1:5000 dilution considered in the results.

In the twenty-eight cases, positive reactions with egg were obtained on seven occasions; with wheat on six; with banana and pork on five; with onion on four; with salmon and celery on three; with almond, walnut, pea, tomato, codfish, apricot, strawberry, grape, rice and beef on two, and with thirteen other foods on one occasion each. With the wheat fractions in 1:5000 dilution positive reactions were obtained with globulin three times, glutenin twice and proteose once. Of the total of twenty-eight cases, twenty-two gave positive reactions with one or more foods and ten gave positive reactions with wheat or one of the wheat fractions.

DISCUSSION

Most allergists agree that skin testing is of very limited value in gastrointestinal allergy since there is apparently little correlation between antibody being fixed in the gastrointestinal tract and antibody being fixed in the skin. However, since, as far as the authors are aware, skin tests with wheat and the wheat fractions have not been reported previously in cases of celiac syndrome which respond to removal of wheat gluten from the diet, it was considered worthwhile to skin test these cases, and look for any correlation between positive skin tests and clinical response.

Examination of the results of the skin tests at once shows that there is very little correlation between the tests and the clinical results. Although wheat gave a positive reaction as often as any other food with the exception of egg, it gave this reaction in only six of the twenty-eight cases and wheat fractions gave positive reactions in four additional cases. Thus only ten cases gave positive reactions to wheat or its fractions while eighteen cases gave negative reactions. Although the incidence of positive wheat reactions is much higher than one would expect in a non-allergic group of children, this correlation is far too low to make skin testing worthwhile as a routine procedure in these cases.

The interpretation of the tests done with the wheat fractions represents a rather complex problem. The protein composition of the several types of wheat varies, but all-purpose patent wheat flour is approximately 10.8 per cent protein[5] of which gliadin represents approximately 3.9 per cent, globulin 0.6 per cent, glutenin 4.4 per cent and proteose 0.3 per cent.[14] Although a 1:1000 dilution of wheat itself is considered suitable for skin testing, the same is not true of the wheat fractions since both the globulin and the proteose gave a large number of positive reactions in both the experimental and control groups when used in 1:1000 dilution, indicating that in this concentration, these fractions are primary irritants. The

results of the tests with 1:5000 dilutions, while not suggestive of primary irritant reactions, give no indication as to which of these fractions is important clinically in these cases, since the positive reactions are so few in number.

In an effort to assess these cases further, histories of allergy in these patients and their families were taken. The twenty-eight patients represent twenty-five families and in twenty-two of these a good direct and collateral family history was obtainable. Of these, seventeen gave a family history of major allergy but only five patients suffered from a major allergy themselves, one with asthma and four with eczema. Family history was not complete in three cases. The series is too small to conclude much from these results, and it can be stated only that allergy is at least as common in these patients and in their families as it is in the general population.

That the celiac syndrome may result from gastrointestinal allergy has been recognized since 1942 when Kunstadter[7] described three cases of typical celiac disease due to gastrointestinal allergy. In two of these patients the symptoms resulted from the ingestion of milk and in the other from milk, wheat and citrus fruits. In two there was a family history of allergy and two had other manifestations of allergy. Since then many other reports of this same association have appeared. McKhann et al[11] reported four more patients with celiac disease due to allergy. These patients had positive skin tests with certain foods and following the elimination of these foods there was improvement both clinically and in the glucose tolerance and fat absorption curves. Block[3] in a discussion of this subject, reported that the foods usually implicated were cow's milk, banana, eggs, orange juice, apple sauce, fish liver oil, chocolate, liver, cereals and vegetables but that cow's milk was the most frequent offender. He made use of the determination of eosinophiles in the stool to differentiate the allergic form of celiac syndrome from the other forms. In 1950 Dicke[6] demonstrated that patients with celiac disease improved when wheat and rye flour were excluded from their diet. Weijers and Kamer[13] demonstrated that there was a decrease in fecal fat when wheat and rye flour were excluded from the diet and that re-introduction of wheat flour, though not of wheat starch, into the diet led to deterioration. McCreary et al[10] also include food allergy as one of the causes of celiac syndrome. They observed a small number of cases where allergy was thought to be the etiological factor, cow's milk being the most common allergen. These latter cases showed spectacular improvement on a milk-free diet. They recommended that every case of celiac syndrome should be given a therapeutic trial for two to three weeks off cow's milk products.

Clein[4], in a report of 140 infants allergic to cow's milk, found that thirty-three or 24 per cent had diarrhea. Several of these thirty-three had been previously diagnosed as having celiac disease, but the symptoms cleared up immediately on elimination of milk from the diet. Anderson et al[2]

reported ten cases diagnosed as celiac disease on clinical, biochemical and radiological evidence. These patients were observed on an entirely wheat-free diet and then wheat flour, wheat starch and wheat gluten were introduced in turn. Effects were assessed by repeating the gastrointestinal studies and by clinical observations. All the children improved clinically when placed on the wheat-free diet. Wheat flour or wheat gluten caused deterioration in their condition but wheat starch did not cause any such deterioration. Kunstadter and Shultz[8] reviewed the literature on allergic celiac disease and reported eleven cases of celiac syndrome, eight of which required the elimination of cow's milk from their diet. Of the eleven cases, eight had a family history of allergy and eight had some other form of allergy. Anderson[1] and Lapin[9] both include gastrointestinal allergy as one of the classifications under celiac syndrome.

SUMMARY AND CONCLUSIONS

Skin tests on twenty-eight cases of celiac syndrome are reported. These skin tests were carried out with forty-seven of the common foods including wheat and with the gliadin, globulin, glutenin and proteose fractions of wheat gluten.

There was no significant correlation between the positive skin tests and the clinical sensitivities.

It is concluded, therefore, that skin testing is of very little value in the etiological diagnosis of celiac syndrome due to gastrointestinal allergy.

REFERENCES

1. Andersen, D. H.; and di Sant'Agnese, P. A.: The Celiac Syndrome. Brennemann's Practice of Pediatrics. Vol. 1, Chap. 29, Page 33, 1948.
2. Anderson, C. M.; Frazer, A. C.; French, J. M.; Serrard, J. W.; Sammons, H. G.; and Smellie, J. M.: Celiac disease: gastrointestinal studies and the effect of dietary wheat flour. Lancet, 1:836, 1952.
3. Block, H.: Celiac syndrome due to gastrointestinal allergy. Arch. Pediat., 66:54, 1949.
4. Clein, N. W.: Cow's milk allergy in infants. Ann. Allergy, 9:195, 1951.
5. Department of Agriculture Bulletin No. 549, Washington, D. C. (June) 1940.
6. Dicke, W. K.: Coeliakie. Utrecht M.D. thesis, 1950.
7. Kunstadter, R. H.: Gastrointestinal allergy and the celiac syndrome. J. Pediat., 21:193, 1942.
8. Kunstadter, R. H.; and Shultz, A.: Gastrointestinal allergy and the celiac syndrome with particular reference to allergy to cow's milk. Ann. Allergy, 11:426, 1953.
9. Lapin, J. H.: Recurrent and chronic diarrhea in infancy and childhood. Am. J. Dis. Child., 67:139, 1944.
10. McCreary, J. F.; Abbott, V.; Pocock, R.; and Brown, A.: The celiac syndrome. Canad. M. A. J., 64:424, 1951.
11. McKhann, C. F.; Spector, S.; and Meserve, E. R.: An association of gastrointestinal allergy with the celiac syndrome. J. Pediat., 22:362, 1943.
12. Sheldon, W.; and Lawson, D.: The management of coeliac disease. Lancet, 2: 902, 1952.
13. Weijers, H. A.; Kamer, J. H. van de: Fat absorption in normal and abnormal infants and children with special reference to coeliac disease. Central Inst. v. voedingsonderzoch. T.N.O. Publication No. 113. Utrecht.
14. Winton and Winton: Structure and Composition of Foods, Vol. III, Wiley, New York, 1937.

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URTICARIA AND ANGIOEDEMA IN CHILDREN AND YOUNG ADULTS

Etiologic and Electrocardiographic Findings in One Hundred Fifteen Cases

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URTICARIA and angioedema, in some instances, present some of the most difficult and perplexing problems that the allergist encounters. The old adage that "the best way to treat an allergic problem is to remove the cause" certainly holds true in these conditions. The recognition of the etiologic factors, however, constitutes one of the major impasses to the successful treatment in many cases. If the etiologic factors are not known to the patient or brought to light by skillful history taking, the cause often goes unknown and the physician must be content to control the symptoms as best he can.

The reasons for the difficulty in establishing the etiology become quite evident when one considers all of the various mechanisms and substances that can be involved. In Table I, a classification of the causes of urticaria and angioedema is listed. The determination of the provocative agent is further complicated by the many routes through which sensitization can take place, and by the fact that multiple etiologic factors can be important in any one case.

TABLE I. AN ETIOLOGIC CLASSIFICATION OF URTICARIA AND ANGIOEDEMA

- I. Foods
- II. Drugs
  - A. Injected
    - 1. Serum
    - 2. Penicillin
    - 3. Others
  - B. Ingested
  - C. Contact
  - D. Inhalant
- III. Contact Allergens Other Than Drugs
- IV. Inhalant Allergens Other Than Drugs
  - A. Pollens
  - B. Perfumes
  - C. Others
- V. Infection
  - A. Acute
  - B. Chronic
  - C. Fungus
  - D. Parasites
- VI. Physical
  - A. Cold
  - B. Heat
  - C. Pressure
  - D. Light
- VII. Psychosomatic
- VIII. Endocrinopathies
- IX. Insects
  - A. Bites
  - B. Contact
- X. Miscellaneous
  - A. Diseases
    - 1. Neoplasms
    - 2. Collagen
    - 3. Others
  - B. Urticaria pigmentosa
  - C. Histamine liberators
- XI. Idiopathic

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Presented at the Decennial Congress of the American College of Allergists, Miami Beach, Florida, April 9, 1954.

Not only is the search for etiologic factors a problem in angioedema and urticaria, but occasionally, when they occur as part of a "serum sickness-like" reaction, the problem of differentiating from acute rheumatic fever and other collagen diseases is present. Since both of these conditions are thought to be forms of hypersensitivity, it is not surprising that there should be some similarity of signs and symptoms. Because of the marked difference in prognosis of the two groups of diseases, it is important to be able to differentiate them as early as possible.

Although no specific tests are available, one of the most useful laboratory examinations in the diagnosis of rheumatic carditis has been the electrocardiogram. It would, therefore, be advantageous to know whether some of the same electrocardiographic changes that occur in rheumatic fever are present in acute and chronic urticaria and angioedema. There is good evidence in both animals and in man that the heart is involved in the pathological process in serum sickness and like reactions,[1,5,6,7,19,26] but a review of the literature reveals few reports of electrocardiographic changes in man. Wadsworth and Brown[25] cite a case of an eleven-year-old boy, who clinically had some evidence of carditis and who had a prolonged PR interval with widening and slurring of the QRS complexes. The authors thought these changes might be due to an atypical serum reaction, but they also suspected that the child had rheumatic fever. Fox and Messeloff[11] later reported transient electrocardiographic changes consisting of lowering of QRS complexes and slight elevation of ST segments. A serum-sickness reaction in a twenty-one-year-old male was described by McKinlay[21] in which marked cardiac enlargement, pericarditis and pleurisy developed and abruptly subsided. Transitory changes in the T waves consistent with the above conditions were recorded in this patient. In a case of acute myocarditis with bundle branch block, Lilienfeld et al[18] believed these transitory changes to be due to sulfonamide sensitivity. Two children, ages four and five, respectively, were reported by Lapin and Mond[16] as having serum sickness-like reactions from penicillin, and among other findings, temporary changes in their electrocardiograms suggestive of myocardial damage. More recently, Foster and Layman[10] reported transient changes resembling acute myocardial infarction in the electrocardiogram of a sixty-five-year-old woman, who had a generalized urticarial rash.

PURPOSE

The purpose of this clinical study was primarily two-fold. First, the authors were interested in obtaining data as to the various causes of urticaria and angioedema in a consecutive series of children and young adults, with particular reference to the role of infection. Secondly, it was considered worth-while to report the results of electrocardiographic findings taken during the acute phases of the urticaria or angioedema.

Other pertinent information regarding age, sex, duration, personal and family incidence of other allergic conditions, and penicillin skin testing results was also obtained.

METHODS

Over a period of one year, consecutive cases of urticaria and angioedema were selected on the basis of typical lesions being present at the time of examination. Possible etiologic factors were investigated as follows: First, a detailed history was taken on a special mimeographed history form by either of the two authors. The form was used so that each history was uniformly complete and the negative findings were easily recorded. Secondly, a complete physical examination was done, which included a scratching of the skin as a crude test for dermographism. A series of laboratory tests were then done as follows: hemoglobin, white blood count and differential, urinalysis, chest X-ray, total eosinophile count, sedimentation rate, throat culture, stools for ova and parasites, anal smear for pinworms, and an electrocardiogram. In chronic cases of urticaria and angioedema, which were defined as those cases lasting longer than one month, additional studies were done as indicated. These included sinus x-rays, dental examination and x-rays, malaria smears, pelvic examinations, urethral smears, biliary tract investigation, basal metabolism tests, agglutinations, blood cultures, and psychiatric consultations. Skin tests to inhalants and foods by the scratch and intradermal methods plus elimination and provocative diets carried out in the more persistent cases. Penicillin urticaria and angioedema reactions were skin tested by both the scratch method, using full-strength crystalline and procaine penicillin, and intradermal method, using 3,000 to 5,000 units of crystalline penicillin per cubic centimeter. Whenever possible and when deemed safe, foods and drugs were given the patient in an attempt to reproduce the lesions.

RESULTS

During the period of study, 115 cases of acute and chronic urticaria and angioedema were investigated. All were thirty-four years of age or younger. Forty children ranging in age from two months to nine years were included. Twenty-three of the children were males and seventeen were females. Because the majority of the remaining patients were members of the United States Air Force, young males ranging in age from seventeen through the twenties made up the bulk of the remaining cases.

Of the one hundred fifteen cases, thirty-nine had chronic symptoms lasting longer than four weeks and seventy-six were acute.

The cases were analyzed as to etiologic factors as shown in Table II.

In five of the cases, it was believed that more than one factor was involved. In addition, there were eighteen patients whose urticaria and angioedema seemed to be aggravated by physical or psychogenic factors.

TABLE II

Etiology	*Number of Cases*
Foods	14
Drugs	
Penicillin	28
Others	9
Contactants	2
Inhalants	2
Infection	12
Physical	3
Psychosomatic	10
Endocrine	1
Insects	3
Undetermined	36

By far, the largest single cause of urticaria and angioedema was penicillin. Twenty-eight cases, 24 per cent of the total number, were attributed to taking penicillin by injection. In most instances, the patient was given either penicillin in oil or procaine penicillin. Nineteen of these patients were skin-tested by the scratch method, and if no reaction occurred, an intradermal test was done. Four gave definite, immediate whealing reactions to the scratch test and a fifth case gave a slight positive reaction. One patient had a positive delayed response. None gave positive reactions to intradermal tests.

An intensive search for evidence of infection or infestation was made. Twelve patients were found to have minimal x-ray evidence of sinusitis, four patients had dental foci of infection, one patient had a cervicitis, and six patients had pinworms. On removal of these infections and infestations, or further observation of the patient, a cause and effect relationship could not be established. However, there were twelve patients in whom an acute infection was thought to play a role either as a predisposing factor or as the direct causative agent. Brief histories of these patients are listed below:

Case 1. H. C., an eighteen-year-old white man, gave a history of headache and nasal congestion alternating with rhinorrhea of three weeks duration. He then suddenly developed a generalized urticarial rash. There was a history of eating shrimp and taking aspirin compound. Physical examination revealed edema and congestion of his nasal mucous membrane with a mucopurulent discharge and a generalized urticarial rash. A white blood cell count was 16,200 with 91 per cent neutrophils and 8 per cent lymphocytes. Culture of the nose and throat revealed no pathogens. A sedimentation rate was 12 mm in one hour. Sinus x-rays revealed a complete opacity of the right maxillary antrum, clouding of the ethmoids and medial frontal cells, and moderate thickening of the left maxillary antrum. One month after his acute sinusitis and hives had subsided, the white count was 10,400 with 48 per cent neutrophils, 48 per cent lymphocytes, 3 per cent monocytes, and 1 per cent eosinophiles. X-rays of sinuses were clear. His sinusitis did not require surgical drainage and had subsided enough by the time diagnosis had been made so that no antibiotics were necessary.

Comment—This boy had, clinically and by x-ray, evidence of an acute sinusitis and concurrently had an acute episode of urticaria. The fact that the two were

present at the same times does not necessitate a causal relationship, but, nevertheless, the circumstances are suggestive. After the urticarial rash and sinusitis had subsided, he was given shrimp and aspirin compound on separate occasions without any reactions.

Case 2. P. E., a thirty-year-old white man, in October, 1953, developed signs of a "cold" without fever. The only medication taken was aspirin. On the following day, he broke out with generalized urticaria and was sent to the allergy clinic. On physical examination, the mucous membranes of the nose were moderately inflamed and the nasal passages contained an excess of mucoid secretions. Typical urticarial wheals were scattered over the body. The rest of his examination was negative. Laboratory studies were non-contributory. The patient was placed on Pyribenzamine®, with good relief of his symptoms. In four days, the urticaria completely disappeared and did not recur with subsequent "colds" or on ingestion of aspirin.

Case 3. C. H., a three-year-old boy, developed a high fever with no other symptoms other than irritability and general malaise. The fever persisted and two days later he developed a severe generalized urticarial rash. A cathartic (Syrup of Pepsin®) and aspirin had been given after the onset of the fever. Physical examination revealed only a generalized urticarial rash with angioedema of the eyes and feet. A white blood cell count was 13,800 with 71 per cent neutrophils, 28 per cent lymphocytes, and 1 per cent monocytes. The remaining laboratory studies were negative. He continued to run fever for three days and the urticaria lasted one week, responding very poorly to different types of antihistamines. Several weeks after his recovery, he was given separate trial doses of both Syrup of Pepsin® and aspirin without the development of urticaria or angioedema.

Case 4. R. B., a seven-year-old white boy, first became ill on August 4, 1953, with a high fever. The following day he broke out with giant urticaria covering the entire body. No medications had been given. About the same time that the hives developed, he began having severe diarrhea. A white blood count was 4,100 with 63 per cent neutrophils, 33 per cent lymphocytes, and 4 per cent monocytes. Other laboratory studies were negative. Within two days the hives disappeared, but the diarrhea persisted for two additional days.

Case 5. C. F., a 20-month-old Negro boy, was seen January 13, 1954, in the pediatric outpatient clinic with an acute pharyngitis. He was treated with Aureomycin® and improved. On January 25, 1954, twelve days later, he was brought back to the clinic with a temperature of 101.8° rectally and a generalized urticarial rash. The child was coughing and a few rhonchi were heard scattered throughout both lung fields. The rest of the physical examination was negative. Laboratory studies revealed a white blood count of 9,000 with 50 per cent neutrophils and 50 per cent lymphocytes. Hemoglobin was 10.0 grams and red cell count 4,500,000. A chest x-ray was normal. The sedimentation rate was 5 mm in one hour. The remaining laboratory studies were normal. The child was put on Benadryl® and was seen the following day. At that time, his temperature had risen to 103°, the respiratory symptoms had become worse, but the hives had improved. Because of the increased severity of the respiratory infection, the child was put on Terramycin®. Two days later, his temperature became normal and the infection rapidly receded. Hives continued to appear for another week, but were easily controlled with Benedryl®.

Case 6. E. F., a three-year-old Negro boy and brother to C. F., was brought to the clinic on January 27, 1954, two days after his brother's onset, with the same presenting complaints of cough, fever, and hives. His history revealed that eleven days before he had completed a course of penicillin for an exudative tonsillitis. He had apparently recovered from this illness, when he developed a cough and fever followed by urticaria and angioedema of the eyes and lips. The only other medication taken prior to the onset of the hives had been a codeine cough mixture. Past history revealed that asthma had been suspected by previous examiners and that he and other members of his family had a sickle cell trait.

On physical examination, typical urticarial wheals were observed along with angioedema of the eyes and lips. A few rhonchi and râles were heard in the bases of both lungs posteriorly. Laboratory findings were as follows: White blood count was 5,400 with 34 per cent neutrophils, 63 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles. Hemoglobin was 10.5 grams. A throat culture showed alpha hemolytic streptococci, and hemolytic staphylococci. The sedimentation rate was 23 mm. Although râles were heard in the lungs, a chest x-ray was interpreted as being normal. A nasal smear for eosinophiles was also negative.

Because findings for E. F. were so similar to those of his brother, C. F., he was treated in a similar manner with Benadryl® and Terramycin®. In twenty-four hours his temperature returned to normal and the chest findings cleared within a few days. The urticaria persisted on and off for one week, but was easily controlled by Benadryl ®.

Comment—In spite of the fact that E. F. received Aureomycin® and his brother, C. F., received penicillin one week prior to the onset of their hives, the occurrence of a new acute respiratory infection followed by urticaria in each of these brothers was so strikingly similar as to indicate a causal relationship.

Case 7. G. V., a four-year-old white boy, was apparently well until November, 1953, when he had what the parents described as a "cold." He recovered from this mild illness without any medication, but one week later developed a generalized urticarial rash associated with high fever and severe diarrhea. The only clue for a possible causative factor, other than the respiratory infection, was that he had a fungus infection of his scalp which had been treated for several weeks with an ammoniated mercury ointment. On physical examination, a patch of alopecia was present on his scalp and his body was covered with giant urticarial wheals. No evidence of a contact dermatitis was present on the scalp. Laboratory studies gave no leads as to etiologic factors; however, he did have a leukocytosis of 11,150 with 68 per cent neutrophils and 32 per cent lymphocytes.

For three days after the onset, this boy continued to have fever and severe diarrhea. His hives were only partially controlled with antihistamines of which several different types were tried. At the present time, four months after the onset, he daily continues to have urticaria which is fairly well relieved by taking Phenergan® at bedtime and Chlor-trimeton® during the day.

Case 8. J. V., a four-year-old white boy, in October, 1953, developed symptoms of the "flu," manifested by fever, vomiting, and diarrhea. That same week the infection appeared in other members of the family. Following this illness, his parents noted that he developed hives. Drugs were never given at any time. On physical examination, several urticarial lesions were observed and some dermographism was present. Laboratory studies revealed a white blood count of 8,160 with 27 per cent neutrophils, 64 per cent lymphocytes, 2 per cent monocytes, 6 per cent eosinophiles, and 1 per cent basophils. His sedimentation rate was 1 millimeter

in one hour. A throat culture showed alpha and beta hemolytic streptococci as predominant organisms. Other laboratory tests were negative.

After the onset, his urticaria appeared almost daily, but was never incapacitating. On January 19, three months after the onset, he was seen in the pediatric clinic with a temperature of 101.2° and with pain in the left ankle. On examination, a generalized lymphadenopathy, some urticarial wheals, and swelling of his left ankle were noted. The fever and the swelling rapidly subsided, and this reaction was interpreted as being a possible "serum sickness-like" reaction. Laboratory work at this time was similar to that originally done. The only change was a drop in his white blood count to 4,800. Since this exacerbation, he has continued to have urticaria almost daily, but has had no further joint manifestations.

Comment—First, the onset of this boy's urticaria seemed to follow an acute gastroenteritis, which could have been etiologic in itself, or paved the way for other factors to come into play. Secondly, the apparent exacerbation of his condition simulated an attack of acute rheumatic fever.

Case 9. M. B., a two-year-old white female, was brought to the pediatric clinic with a history of diarrhea, cough, nasal stuffiness and fever twenty-four hours prior to the onset of her hives. Other members of the family had a similar respiratory infection. Two weeks before the onset, a booster diphtheria-pertussis-tetanus immunization injection was given. Physical examination revealed an inflamed pharynx, a mucoid nasal discharge, generalized urticarial lesions, and angioedema of both hands and feet. With the exception of an elevated white blood count of 13,450 with 32 per cent neutrophils and 68 per cent lymphocytes and an elevated sedimentation rate of 50 mm. per hour, all laboratory studies were negative. The urticaria and angioedema, which lasted one week, were effectively controlled by Pyribenzamine®.

Case 10. J. D., a one-year-old white boy, was brought to the clinic with a history of a cough and nasal discharge of two weeks' duration. Three days before being seen, he broke out with hives. The only drug that had been given was aspirin and camphorated oil had been rubbed on his chest. On physical examination, a mucopurulent green nasal discharge was present along with generalized urticarial wheals. Laboratory studies showed a white blood count of 12,850 with 28 per cent neutrophils, 65 per cent lymphocytes, 2 per cent monocytes, 5 per cent eosinophiles, and 2 per cent basophils. Other laboratory studies were negative. He was treated with Benadryl® and Terramycin®, with good results, and after one week the urticaria and infection had disappeared. This child has since been given aspirin without any untoward effects.

Case 11. S. S., a two-year-old white girl, was brought to the pediatric clinic with a two-day history of cough and fever followed by the development of an urticarial rash. The child was given some aspirin because of the fever and the hives. On physical examination, small urticarial wheals were scattered over the body. An excessive amount of mucopurulent material was present in the nose. The rest of the examination was essentially negative. Laboratory results showed a white count of 15,000 with 82 per cent neutrophils and 18 per cent lymphocytes. A sedimentation rate was 13 mm. in one hour. Cultures of the blood and throat revealed no organisms. Chest x-ray was negative.

The hives and coughing persisted for about five days, but the former was adequately controlled with Benadryl®. Because the cough became worse and she developed bilateral otitis media while under observation, Terramycin® was started and was followed by a rapid recovery.

Case 12. A. B., a seven-year-old white girl, in May, 1953, developed a sore throat, which was treated with Terramycin®. About four days after the onset, transient swelling of the knees, ankles and wrists developed. These swellings continued for several days and then subsided. She had no further trouble until July, 1953, when swelling of the fingers of her left hand recurred. No fever was present. For the next several months she continued to have pain and transitory swelling of the joints and on several occasions, was observed with definite angioedema of the lips, fingers, hands and feet. At these times, she seemed to respond to antihistamines. On many physical examinations, the only positive findings noted were the non-tender swollen joints and angioedema. Her pulse was never rapid, usually around 80, and the blood pressure was 90/60 mm. mercury. No murmurs or cardiac enlargement were found. A white blood count was 8,900 with 34 per cent neutrophils, 65 per cent lymphocytes, 1 per cent monocytes, and 1 per cent eosinophiles. Sedimentation rate was 17 mm. in one hour. Cardiac fluoroscopy and electrocardiogram were normal.

The patient was last seen in March, 1954, at which time she was still having sporadic episodes of angioedema with and without joint involvement which were adequately controlled with Benadryl®.

Comment—This girl's case, particularly in the first few days after onset, represented a problem of differential diagnosis. Although by the subsequent course of this patient's illness and by laboratory data, the diagnosis of angioedema was quite easily made, the similarity of symptoms and findings to rheumatic fever was so striking, that she was one of the cases that stimulated the authors to study electrocardiograms in other patients with urticaria and angioedema.

Ninety-eight patients had electrocardiograms done during the acute phases of urticaria and angioedema. Only one patient had an abnormal electrocardiogram. Repeated tracings and cardiac studies over a period of two months revealed the abnormality to be typical of a Wolff-Parkinson-White syndrome. One other patient, a thirty-one-year-old Negro Airman, had a borderline normal electrocardiogram in that his T waves in lead two were diphasic, RST segment elevated in leads V_3 and V_4, and low T waves in V_5 and V_6. These findings persisted over a period of two months without significant change and have been recently described by Goldman[12] as being a normal variant occurring more frequently in the Negro race. In both of these cases, the authors believed that any abnormalities existing were present before the onset of the urticaria or angioedema and in no way were related.

The histories of the entire group were further analyzed as to the incidence of other atopic conditions—pollinosis, asthma, allergic rhinitis and eczema—in the patients and their families. In four of the 115 cases of urticaria and angioedema, the information was not entirely complete and was therefore not included in this tabulation. Twenty of the remaining 111 patients, or 18 per cent, had a history of other allergies and thirty-one, or 28 per cent, came from allergic families. It is significant that among the patients who developed urticaria or angioedema from penicillin, only two of twenty-six, or 8 per cent, had other allergic conditions and five, or 19 per cent, had a positive family history.

DISCUSSION

Some of the manifold reasons for the difficulty in discovering the etiologic factors in urticaria and angioedema were pointed out earlier. These were the almost unlimited number of substances which can, through varied routes, lead to these conditions; multiple factors being present in some cases; and very often the lack of specific diagnostic aids. Keeping these points in mind, it is not surprising that the cause of the urticaria or angioedema was undetermined in thirty-six, or almost one-third of the total 115 patients.

Even if one is suspicious of certain substances as determined by history, it is often impossible or dangerous to prove conclusively that the substance is the culprit in question. For example, a patient who has received penicillin ten days prior to the onset of hives and swollen joints almost certainly is having "serum sickness" due to the penicillin, yet one would be hard pressed to prove it. Skin tests in the delayed penicillin reactions as was evident in our cases and as others have reported in the past,[4] are very variable and usually negative. To inject the patient with more penicillin would certainly be extremely dangerous and, even then, might not give the expected reaction.[20,23]

When one gets into the realm of infectious, endocrine and psychic factors, one is treading on more hazardous grounds in trying to prove them as cases of urticaria and angioedema.

One of the purposes of this clinical study was to try to correlate the role of infection, both acute and chronic, as causative factors. That such a relationship does exist has been pointed out by several authors in the past, and as a matter of fact, was even thought to be one of the most common causes of chronic urticaria. Barber[2] cites six cases of chronic urticaria which he thought were due to a streptococcic infection. Eichenlaub[8] attributed 24 per cent of his cases to foci of infection. Menagh[22] in 1928 stressed the fact that 48.8 per cent of his 129 cases of urticaria had biliary tract diseases and that this disorder played an important role as a cause of urticaria. In review of 170 cases, Fink and Gay[9] indicated that fifty-two, or 30 per cent of their cases, were due to infection. They listed chronic tonsillitis, oral sepsis and sinusitis as the most common type of infection in these patients. Hopkins and Kesten[14] in a study of 200 patients with urticaria attributed fourteen cases to chronic infection. Realizing the complex nature of urticaria, Stokes et al[24] reported that 43 per cent of their patients had evidence of foci of infection, but they were unable to prove an etiologic connection. A report by Leriche[17] implicated acute appendicitis in two cases with disappearance of the urticaria following appendectomy. Winkenwerder[27] described a case of urinary infection as a cause of chronic urticaria. In 1938, Hansen-Prüss[13] reported that he had evidence that beta hemolytic streptococci in the respiratory tract or

duodenum caused urticaria in eleven individuals. More recently, Bivings[3] reported twenty-two cases with acute infections of the throat, ears and urinary tract as a cause of urticaria and angioedema in children.

In this series of 115 cases of urticaria and angioedema, the authors considered acute infections, mostly respiratory in nature, to be either etiologic or contributory in twelve cases. A cause-and-effect relationship was not proven in any of these patients; however, the circumstances surrounding the onset in each of these patients does strongly suggest that the infection played a major role.

The authors are well aware of the many pitfalls in making such an assumption. Some of these pitfalls are as follows: First, "serum sickness-like" reactions and other allergies can simulate acute infections and be mistaken for the cause rather than as manifestations of the hypersensitivity reaction. Secondly, today most infections are treated with many drugs which in themselves could cause hypersensitive reactions. Thirdly, in humans it is almost impossible to reproduce the same set of infectious and immunologic circumstances that initially led to the patient's urticaria or angioedema. Fourthly, removal of an infection and subsidence of the symptoms does not establish a causal relationship. In spite of these objections and many more, the clinical observation of an infection followed by urticaria and angioedema indicates a relationship that cannot be denied.

The mechanism by which these infections produce these lesions is not known. It is conceivable that an antigen-antibody reaction is present, as in most other hypersensitivity reactions, or that a non-specific release of histamine or other substances is brought about by the infection. In three of the cases, the urticaria was associated with an acute gastroenteritis, and it is plausible that an increased permeability of the bowel was produced so as to allow unaltered proteins or other substances to gain entrance into the body. Others, even as early as 1908, have made similar observations on the relationship of gastrointestinal disturbances and sensitivity reactions.[15]

In a review of the literature on the subject of the relationship of infection to urticaria and angioedema, it was noted that the great emphasis has been on bacterial foci of infection. Very little mention is made of the possible role of virus infections. Although direct proof is lacking, in several of the cases—P. E., C. F., E. F., J. V., M. B., J. P.—viral infections were very likely present, and were probably the etiologic agents involved.

To the authors' knowledge, this is the first report of electrocardiograms taken in a consecutive series of patients with urticaria and angioedema. The absence of electrocardiographic changes in the ninety-eight patients in this study indicates that cardiac abnormalities that have been described with serum sickness, urticaria and similar hypersensitive reactions are probably rare. This information should be helpful in differentiating these conditions from the so-called collagen diseases.

SUMMARY AND CONCLUSIONS

The results of an investigation for etiologic factors in a consecutive series of 115 children and young adults with urticaria and angioedema are given.

Penicillin was found to be the most common cause, being responsible for twenty-eight of the cases (24 per cent). Nineteen of these patients were skin tested with penicillin and only five gave positive reactions. It is concluded that penicillin skin tests are of little value in determning delayed penicillin reactions.

In fourteen patients (12 per cent), the cause of their urticaria and angioedema was foods.

Infection was considered to be the primary or initiating factor in twelve patients (10 per cent). Brief histories of these patients are recorded. Although not proven, the histories of six of these patients strongly suggest an acute viral infection as the cause of urticaria or angioedema.

In thirty-six of the patients (31 per cent), the etiology could not be determined. This serves to re-emphasize that our present methods of investigating etiologic factors are inadequate and that large gaps exist in our knowledge of urticaria and angioedema.

An analysis of personal and family histories for other atopic conditions is given. Eighteen per cent gave positive personal histories and twenty-eight per cent came from allergic families. In the penicillin-sensitive group, only eight per cent gave positive personal histories and nineteen per cent had positive family histories.

The results of electrocardiograms taken during the acute phases of the urticaria or angioedema in ninety-eight patients are also presented. An abnormal EKG characteristic of a Wolff-Parkinson-White syndrome was found in one patient. A variation of the normal was found in one other case. None of these changes could be attributed to the urticaria or angioedema, and it is concluded that pathological changes in the heart as manifest by abnormal EKGs are rare in these conditions.

REFERENCES

1. Auer, J., and Robinson, G. C.: An electrocardiographic study of the anaphylactic rabbit. J. Exper. Med., 18:450, 1913.
2. Barber, H. W.: Chronic urticaria and angio-neurotic oedema due to bacterial sensitisations. Brit. J. of Derm. and Syph., 35:209, 1923.
3. Bivings, Lee: Acute infectious urticaria. J. Ped., 28:602, 1943.
4. Boger, W. P., Sherman, W. B.; Schiller, I. W.; Siegel, S.; Rose, B.; Edited by Schiller, I. W.: Allergic reactions to penicillin. J. Allergy, 24:383, 1953.
5. Boughton, T. H.: Vascular lesions in protein intoxication. J. Immunol., 2:501, 1917.
6. Clark, E., and Kaplan, B. I.: Endocardial arterial and other mesenchymal alterations associated with serum disease in man. Arch. Path., 24:458, 1937.
7. Criep, L. H.: Electrocardiographic studies of the effect of anaphylaxis on the cardiac mechanism. Arch. Int. Med., 48:1098, 1931.
8. Eichenlaub, F. J.: Etiology of urticaria and allied dermatoses. Annals Clin. Med., 4:170, 1925.
9. Fink, A. I., and Gay, L. N.: A critical review of 170 cases of urticaria and

angio-neurotic oedema followed for a period of from two to ten years. Bull. Johns Houkins Hosp., 55:280, 1934.
10. Foster, R. F., and Layman, J. D.: Generalized urticaria with electrocardiographic changes simulating myocardial infarction. J.A.M.A., 148:203, 1952.
11. Fox, T. T., and Messeloff, C. R.: Electrocardiographic changes in a case of serum sickness due to tetanus antitoxin. New York State J. Med., 42:152, 1942.
12. Goldman, M. J.: RS-T segment elevation in mid- and left precardial leads as a normal variant. Am. Heart J., 46:817, 1953.
13. Hansen-Prüss, O. C.: Urticaria of bacterial origin. J. Allergy, 9:577, 1938.
14. Hopkins, J. G., and Kesten, B. M.: Urticaria, etiologic observations. Arch. Derm. and Syph., 29:358, 1934.
15. Hutinel, V.: Intolerance pour le lait et anaphylaxie chez les nourrissons. Clinique, Paris, 3:227, 1908.
16. Lapin, J. H., and Mond, I.: Serum sickness-like syndrome from penicillin. Am. J. Dis. Child., 82:335, 1951.
17. Leriche, R.: Guerison definitive d'urticaire a type anaphylactique a la d'appendicectomie. Presse Med., 44:916, 1936.
18. Lilienfeld, A.; Hockstein, E., and Weiss, W.: Acute myocarditis with bundle branch block due to sulfonamide sensitivity. Circulation, 1:1060, 1950.
19. Longcope, W. T.: The relationship of chronic protein intoxication in animals to anaphylaxis. J. Exper. Med., 22:793, 1915.
20. Lyons, C.: Penicillin therapy of surgical infections in the U. S. Army. J.A.M.A., 123:1007, 1943.
21. McKinlay, C. A.: Allergic carditis, pericarditis and pleurisy; report of case of serum sickness with predominant cardiac manifestations and symptomatic recovery. J. Lancet, 68:61, 1948.
22. Menagh, Frank R.: The etiology and results of treatment in angio-neurotic edema and urticaria. J.A.M.A., 90:668, 1928.
23. Siegel, S.: Allergy to penicillin O and management of penicillin sensitivity. Am. J. Med., 11:196, 1951.
24. Stokes, J. H.; Kulchar, G. V., and Pillsbury, D. M.: Effect on the skin of emotional and nervous states, Etiologic background of urticaria with special reference to the psychoneurogenous factor. Arch. of Dermat. and Syph., 31:470, 1935.
25. Wadsworth, G. H., and Brown, C. H.: Serum reaction complicated by acute carditis. J. Ped., 17:801, 1940.
26. Wilcox, H. B., Jr., and Andrus, E. C.: Anaphylaxis in the isolated heart. J. Exper. Med., 67:169, 1938.
27. Winkenwerder, W. L.: The relationship of urticaria and angio-neurotic edema to general medicine. Penn. M. J., 43:1073, 1940.

ONE HUNDREDTH ANNIVERSARY OF DISCOVERER OF ADRENALIN

The late Dr. Jokichi Takamine was lauded on the one hundredth anniversary of his birth, at Kanazawa, Japan, November 3, 1953, for his scientific discoveries, international trade contacts and great humanitarian interests. Greatest of all Takamine discoveries was his isolation in 1900 of Adrenalin, the first pure crystalline hormone to be made available to the medical profession.

MOLD FUNGI IN THE ETIOLOGY OF RESPIRATORY ALLERGIC DISEASES

XV. Selection of Molds for Therapy

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SPECIFIC etiological diagnosis in inhalant mold allergy involves many considerations which must constantly be borne in mind for proper clinical evaluation and logical selection of therapeutic antigens. Not only must the allergist appreciate the significant dominant and occasionally occurring allergenic fungus species of the patient's particular geographic area, but he must anticipate additional forms encountered in the patient's home, occupation or travel. Furthermore, he must consider botanical relationships between the various appropriate molds in a critical evaluation of the diagnostic findings. Finally, specific, reliable, potent and non-irritating extracts must form the basis of all worthwhile testing and treatment. In this paper we hope to emphasize these and other essential points which we consider fundamental in a scientific approach to the problem.

GEOGRAPHIC DISTRIBUTION

Skin testing with antigens of molds selected according to their known geographic distribution and seasonal incidence, with flexibility for environmental problems, is mandatory for adequate diagnostic study of inhalant mold sensitive patients, and becomes a logical part of the clinical investigation to be performed when indicated by the history.

Sufficient survey data are now available to permit an adequate selection of diagnostic and therapeutic mold antigens for most sections of the Continental United States. Of all the common allergenic molds the *Fungi Imperfecti (Deuteromycetes)* are of most clinical importance, and, of these, the genera of the dematiaceous group (Table I) are usually found in greatest numbers. With the exception of *Helminthosporium*, *Curvularia* and *Spondylocladium*, which occur principally in the South, molds of the *Dematiaceae*, especially *Alternaria* and *Hormodendrum*, occur in all areas where surveys have been conducted and often make up the greater part of all molds ordinarily present in routine atmospheric sampling. While molds of other groups of the *Fungi Imperfecti*, such as the *Moniliaceae* (comprising numerous species of *Aspergillus, Penicillium, Paecilomyces, Monilia, Mycogone, Botrytis, Gliocladium,* and

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Presented at the Decennial Congress of the American College of Allergists, Miami Beach, Florida, April 8, 1954.

Trichodema), the *Tuberculariaceae (Fusarium)*, and the *Sphaerioidaceae (Phoma)*, as well as the *Mucorales (Mucor* and *Rhizopus)* of the *Phycomycetes*, and representative species of the *Ascomycetes* seem equally widespread as atmospheric inhabitants, they are usually present with less regularity and in somewhat smaller numbers. In particular areas, on the other hand, any of these molds may appear in high concentration, thereby suggesting local factors of habitat or adaptability. Other fungi, particularly the *Basidiomycetes*, of which probably the best known are the smuts and rusts, may be clinically significant in certain sections. Those species which parasitize certain cereal grains may occur, in particular seasons, in sufficient concentration in the grain growing areas to constitute definite clinical problems. Technical difficulties probably account for the paucity of clinical information available about this entire group. It is not unlikely that further investigations will reveal species of *Basidiomycetes* to be even more widespread and of greater clinical significance than is now suspected.

It is well known that season, temperature and humidity exert significant and predictable influences on mold growth, resulting in higher perennial mold populations in the southern more temperate zones, as contrasted with a definite seasonal incidence in the north where climatic extremes depress in the winter but promote mold growth in the summer. Many reports have[2,5,6,9,14,15] stressed the "mold season" in late summer and fall, particularly in the midwestern and central portions of the country where the problem has been most extensively studied. In some regions, particularly the Pacific Northwest,[8] mold antigens which seem adequate generally for other sections do not appear to react significantly on patients presumed to be mold sensitive. Further survey studies and clinical correlation are in these instances urgently necessary.

BOTANICAL CLASSIFICATION

Table I is a list of the culturable mold fungi embodying those species encountered with sufficient regularity in survey studies to be considered representative of the air populations throughout most of the United States where adequate data have been obtained. This array of mycological terminology would appear most formidable and even discouraging except for the fact that conventional botanical classification affords helpful grouping of related genera and species. Just where the significant groups might be defined and particularly what species should be included as respective group representatives are matters of great importance.

Multiple sensitization to several related species or genera is most striking insofar as the most frequently reacting group of molds, the *Dematiaceae*, is concerned. It is a matter of common knowledge that when one species of a genus, such as the genus *Alternaria*, of this family reacts on a sensitive patient, species of one or more of the other genera may react similarly. On the other hand, only one species may react, and in such

TABLE I. CULTURABLE MOLD FUNGI

FUNGI IMPERFECTI
- Dematiaceae
  - Alternaria tenuis
  - Curvularia spicifera
  - Spondylocladium sp.
  - Helminthosporium interseminatum
  - Hormondendrum cladosporioides
  - Stemphylium botryosum
  - Nigrospora sphaerica
  - Pullularia pullulans
- Moniliaceae
  - Aspergillus fumigatus
    - A. flavus
    - A. glaucus
    - A. nidulans
    - A. niger
    - A. sydowi
    - A. terreus
  - Botrytis cinerea
  - Gliocladium fimbriatum
  - Monilia sitophila
  - Mycogone nigra
  - Paecilomyces varioti
  - Penicillium atramentosum
    - P. biforme
    - P. intricatum
    - P. carmino- violaceum
    - P. luteum
    - P. notatum
  - Trichoderma viride
- Sphaerioidaceae
  - Phoma herbarum
- Tuberculariaceae
  - Fusarium vasinfectum

PHYCOMYCETES
- Rhizopus nigricans
- Mucor racemosus

ASCOMYCETES
- Saccharomycetaceae
  - Saccharomyces cerevisiae
- Torulaceae
  - Rhodotorula sp.
- Chaetomiaceae
  - Chaetomium sp.

an instance the isolated reaction is often to some species of *Alternaria*, as *Alternaria tenuis;* indeed, *Alternaria* may be the only allergen not only of the *Dematiaceae*, but even of the entire mold list, to react. This fact has doubtless been responsible for many allergists employing *Alternaria* as the sole representative of the entire dematiaceous group, or together with one or two other fungi, usually a species each of *Penicillium* and *Aspergillus*, for their entire mold testing armamentarium.

Other botanical mold categories may show distinct group allergenicity. For example, both *Mucor* and *Rhizopus*, which we employ as representatives of the *Mucorales*, generally produce similar reactions. Among the *Moniliaceae*, furthermore, definite reaction patterns are frequently striking; such relationship may occasionally extend essentially to the entire family, but more often it is limited to several species of a single genus, as *Aspergillus* or *Penicillium*, or to species of several genera. In view of the fact that there are so many species of *Aspergillus* and *Penicillium*, we have endeavored to select representative morphological types of these genera for our routine testing, in order to permit a multiplicity of reactions within these respective series.

Our enthusiasm at one time prompted us to pool various species and genus representatives into appropriate testing mixtures in the hope that the botanical groups thus approximated would be more diagnostic than the single species individually. While these mixtures produced definite reactions, we soon discarded them because we preferred the additional corroboration of positive reactions from other species of the same genus or of related genera.

About twelve years ago we concluded, on the basis of experiments involving neutralization of passively sensitized sites with our then avail-

able conventional type antigens, that *Alternaria* would exhaust reagins for all other dematiaceous fungi. On the other hand in these studies we did not encounter a single instance in which another dematiaceous mold exhausted the reagin for *Alternaria*.[11] Using our more active acetone precipitated allergens we have subsequently restudied this problem by both *in vitro* and *in vivo* neutralization experiments,[12] with the conclusion that the dematiaceous molds contain common family as well as specific genus allergens and that *Alternaria* is not a universal dematiaceous allergen. On the contrary, in these later studies we discovered instances in which *Alternaria* failed to exhaust reagins for at least three other dematiaceous molds *(Helminthosporium, Spondylocladium* and *Curvularia),* and in one experiment the genus *Curvularia* exhausted reagins for all molds in the family including *Alternaria.* Following this evidence that a single "key" species does not exist for the *Dematiaceae,* the most likely group among all the molds where such immunological relationship might occur, we have regarded as significant all genera and species giving definite skin tests, especially when the reacting molds are confined to botanical groups.

One significant exception, however, occurs in the parallelism between reactions to species of both *Alternaria* and *Phoma.* For many years we have noticed that when *Alternaria tenuis* reacts positively, *Phoma herbarum* produces almost identical reactions by scratch or punch tests, as well as by intradermal titrations. *(Alternaria tenuis* and *Phoma herbarum* are the species we use in our work.) This similarity in reaction pattern for these two species, noted frequently with our earlier conventional type extracts, is observed now almost uniformly with our acetone precipitated antigens. In fact, we have come to *expect* a reaction with *Phoma* if *Alternaria* has reacted, and vice versa. Even though *Phoma* is thus an indispensable antigen on our testing tray, we do not employ it therapeutically, but use it solely to confirm reactions to *Alternaria.*

That a somewhat close immunological parallelism between *Alternaria* and *Phoma* does exist, however, is not without precedent. A possible relationship between the imperfect genera, *Phoma* and *Alternaria,* and a common perfect form, *Pleospora,* has been suggested by a number of workers (Benham,[1] Neergaard,[10] and Butler and Jones[4]). The work of Neergaard, and Butler and Jones would indicate that some species or strains of both *Alternaria* and *Phoma* form *Pleospora* as their perfect stage, which certainly suggests that they may be rather closely related botanically.

Benham's report is significant not only for the botanical relationship suggested between *Alternaria* and *Phoma,* but in the fact that her interest in this phase of the study of these two fungi developed following a clinical observation. She was able to induce asthmatic attacks in a patient by the use of an extract of *Phoma* obtained from a plate that had been exposed where the patient's attacks were most severe. As indicated in

the case history, the patient had been shown to be most sensitive to *Alternaria*.

Alternaria and *Phoma* might well be investigated further, both clinically and from a botanical point of view.

TYPES OF ANTIGENS

The method of extraction in the preparation of mold allergens determines to a great degree the specificity, potency and freedom from irritating properties of the antigens produced. For several years we employed conventional type extracts, prepared essentially by saline or glycerosaline extraction of the dried mold pellicles. Skin tests with such allergens were always difficult to interpret in all except extremely sensitive patients, because of the high percentage of nonspecific reactions resulting frequently from the necessary use of relatively concentrated solutions. As we now review the records of our earlier mold patients, we feel that many of them were regarded as mold sensitive on the basis of nonspecific positive reactions. Ultimately we appreciated this situation and attempted to correct it by passive transfer studies in questionable cases which seemed to occur with great regularity, but even with this technique we were occasionally still in doubt. In 1942 Browning,[3] in a critical study of our antigens, reported that their diagnostic value was very low. Although some of the conventional type extracts may have been reliable to a limited extent, particularly for highly sensitive patients, the antigens were so lacking in uniformity that with their use adequate patient evaluation was problematical.

About 1946 we began studying the acetone precipitated extracts developed by The Association of Allergists for Mycological Investigations[13] and since 1950 we have employed these "type 33" antigens altogether in our skin tests. With these allergens, which seem singularly free from nonspecific irritating properties,[7] the number of false positive reactions is reduced materially. Furthermore, the acetone precipitated extracts contain active allergenic factors in such high concentration that scratch or punch tests react specifically and vigorously, and positive intradermal tests frequently react in dilutions of 1:10,000 or higher. This regularity with which positive scratch or punch tests can be correlated with positive intradermal tests, often in high dilutions, has impressed us as one of the most outstanding features of these antigens, which, with their greater specificity, no doubt has contributed appreciably to their diagnostic reliability.

We feel that we should mention here one particular observation in connection with the acetone precipitated mold extracts. We have noted in an unusually high percentage of treated patients that subsequent retesting reveals significant diminution in skin reactivity as compared with the pretreatment reactions. At first we suspected this lessened reactivity in treated patients as indicating decreased potency in subsequent extract

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lots, but it has been observed even with the same lot, and by so many of our collaborators using the antigens, that we believe we are in some way dealing with an unusual degree of specifically reduced skin response. We offer no explanation for this observation, which we merely mention because it must be borne in mind in interpreting tests on treated patients.

COMBINATIONS FOR THERAPY

Aside from the diagnostic help afforded by multiple reactions to appropriately selected mold test antigens as outlined above, another consideration demands that testing and treatment with fungus allergens be conducted with as many representative species as is conveniently expedient. This is the fact that the number of species in many genera hopelessly exceeds those species for which extracts are actually available, and by the same token some significant genera are doubtless not even represented in diagnostic and therapeutic antigens. It would be physically impossible to test with all mold fungi, or perhaps to combine all reacting species into treatment mixtures, even if the antigens were available. Consequently, one can only hope that considerable cross sensitization might exist, otherwise clinical results from treatment with the commonly employed molds would not be as successful as it is. At the same time, universal cross immunity cannot be anticipated among all the molds; therefore, expediency would dictate that treatment mixtures be made as polyvalant as possible.

Here again one must recognize practical limitations. In actual practice we have found that pooling of related species in keeping with recognized botanical categories affords workable therapeutic mixtures. Thus in instances of positive reactions to several genera of the *Dematiaceae*, we would include them all in a therapeutic dematiaceous mixture. Similiarly we would prepare all species of the moniliaceous molds giving definite reactions in a moniliaceous mixture if the reactions in several genera suggested sensitization to the entire family, or we might consider a genus mixture, if several species of a genus, as for example, *Penicillium*, indicated sensitization to that genus. In the same way we would combine *Mucor* and *Rhizopus* into a *Mucorales* mixture, and so on. Occasionally, though not in keeping with botanical classifications, we have combined unrelated species when reactions suggested they were of minor importance, in comparison with reactions of more definite significance.

In instances of multiple reactions confined to a definite botanical category, our experience has been that treatment mixtures containing all the reacting molds have often afforded better clinical results than have single species antigens. Our not infrequent observation of improvement following the addition of botanically related reacting species to previous therapy with a single species has particularly emphasized the superiority of such treatment combinations. On the other hand, we occasionally observe positive reactions to several mold antigens of more than one botani-

cal division, for example, to species of both *Dematiaceae* and *Moniliaceae*. While we feel that multiple reactions with acetone precipitated extracts are specific, we are sometimes still at a loss to know whether all the reacting groups are clinically significant. In the interest of conservatism we have in such instances employed therapeutically what appeared to be the major reacting group first and later have added mixtures from additional mold categories when clinical symptoms persisted. At the same time in mold problems wherein significant seasonal or environmental contact with species of more than one major botanical group seemed probable we have proceeded from the start with the appropriate separate therapeutic combinations.

Our feeling on the point of maintaining mold mixtures in appropriate combinations on botanical consideration might be likened to the familiar clinical experience that botanically related pollens are generally best combined into separate treatment mixtures. For example, we keep grass pollen mixtures separate from ragweed pollen mixtures, although both our ragweed and grass treatment mixtures generally are as polyvalant as we can make them.

During the routine hyposensitization period, it is of great importance to regard mold combinations prepared on the botanical criteria outlined above as separate and distinct antigens. Difficulties arising from improper dosage can quite readily be appreciated by alternate manipulation of these various mixtures; the mixtures themselves seldom require breaking down for more detailed readjustment. Ultimately, when dosage requirements and limitations become obvious and the program is stabilized, all the mold mixtures may be combined in proper ratio for maintenance injections.

SUMMARY

1. Appropriate diagnostic and therapeutic mold antigens must be selected on the basis of geographic and seasonal incidence and must be adapted to particular areas.

2. Diagnostic and therapeutic mold antigens of reliable potency and freedom from irritating properties are essential.

3. Mold reactions should be evaluated on the basis of botanical classification.

4. Appropriately combined mold mixtures representing botanical groups are preferable for treatment.

REFERENCES

1. Benham, Rhoda W.: Phoma conidiogena, an excitant of asthma: Some observation of the development and cultural characteristics. Bull. Torrey Botanical Club, 58 (4) :203-214 (April) 1931.
2. Blumstein, George I, and McReynolds, S. U.: Mold allergy. I Field survey of Philadelphia area. J. Allergy, 16:285, 1945.
3. Browning, W. H.: Mold fungi in the etiology of respiratory allergic diseases. II Mold extracts—A statistical study. J. Allergy, 14:231, 1942.
4. Butler, Sir Edwin John, and Jones, S. G.: Plant Pathology. Macmillan & Co., Ltd., London, 582. 1949.

5. Collier, Thomas W., and Ferguson, Betty Anne: Airborne fungus spores, Brunswick, Georgia, area. Incidence and variation with climatic changes. Ann. Allergy, 11:480, 1953.
6. Feinberg, Samuel M., and Little, Harold T.: Studies on the relation of microorganisms to allergy. III A year's survey of daily mold spore content of the air. J. Allergy, 7:149, 1936.
7. Figley, Karl D., and Rawlings, Frank F. A.: Mold fungi in the etiology of respiratory allergic diseases. XIII The use of a concentrated extract in the treatment of mold-sensitive patients. Ann. Allergy, 7:610, 1949.
8. Moore, Merle: Personal Communication.
9. Morrow, M. B., Lowe, E. P., and Prince, Homer E.: Mold fungi in the etiology of respiratory allergic diseases. I A survey of air-borne molds. J. Allergy, 13:215, 1942.
10. Neergaard, Paul: Danish Species of Alternaria and Stemphylium. Einer Munksgaard, Copenhagen, 387, 1945.
11. Prince, Homer E.: Unpublished.
12. Prince, Homer E., Arbesman, Carl E., Sellers, Earl D., Petit, Paul T., Brown, Ethan Allan, and Morrow, Marie B.: Mold fungi in the etiology of respiratory allergic diseases. XII Further studies with mold extracts. Ann. Allergy, 7:597, 1949.
13. Prince, Homer E., Epstein, Stephan, Figley, Karl D., Wittich, Fred W., Henry, L. Dell, and Morrow, Marie B.: Mold fungi in the etiology of respiratory allergic diseases. IX Further studies with mold extracts. Ann. Allergy, 7:301, 1949.
14. Report of the subcommittee on mold survey of the research council, American Academy of Allergy for the season of 1949. J. Allergy, 21:455, 1949.
15. Wallace, M. Elizabeth, Weaver, R. H., and Scherago, M.: A weekly mold survey of air and dust in Lexington, Kentucky. Ann Allergy, 8:202, 1950.

Medical Arts Bldg.

POLLEN SURVEYS

Those members in foreign countries, as well as in Canada and the United States, who live in areas where they think a detailed survey may add to information on the area distribution of pollens, will find helpful the chapter in Sheldon's "A Manual of Clinical Allergy" (Saunders) by O. C. Durham, Secretary of the Pollen Survey Committee, Abbott Laboratories Research Division, Chicago, Illinois. In this chapter Durham pictures all the more common types of pollen encountered in aerobiologic studies. Figures showing pollen grains, both as photomicrographs and drawings, serve to bring out the key characters of the different genera. Each plate is accompanied by a full page of explanatory notes. It is a very practical approach for one who is interested in the pollen problems of allergy.

There is available a technique for counting pollen grains as approved by the Research Council of the American Academy of Allergy, and on request interested allergists can receive a complete copy of the Pollen Survey Committee's report for the past season, together with statistical information and information concerning the sampling instrument.

When one has completed the study of Sheldon's manual, he will be ready for the technical work of Dr. Wodehouse. Dr. Wodehouse has written two books: The first, "Pollen Grains," published by McGraw-Hill, is a technical treatise on the morphology of pollen grains (mostly wind-borne). The illustrations are all drawings, mostly surface characters. His other book, entitled "Hay Fever Plants," was published in 1945. The illustrations in this book are very similar to those in his larger, more technical book.

A comprehensive atlas of pollen grains does not exist. The nearest approach is

(Continued on Page 283)

SURVEY OF AIRBORNE POLLEN AND MOLD SPORES IN ISRAEL, 1953

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THIS is a survey of slide observations of the atmospheric incidence of pollen and mold spores in Israel in the year 1953, taken in the center of the town of Tel Aviv-Jaffa.

For details, methods of counting, counted slide area and signification of the numbers, see the previous communications covering the years 1951 and 1952 as published in ANNALS OF ALLERGY, Pages 322-328 (May-June) 1953.

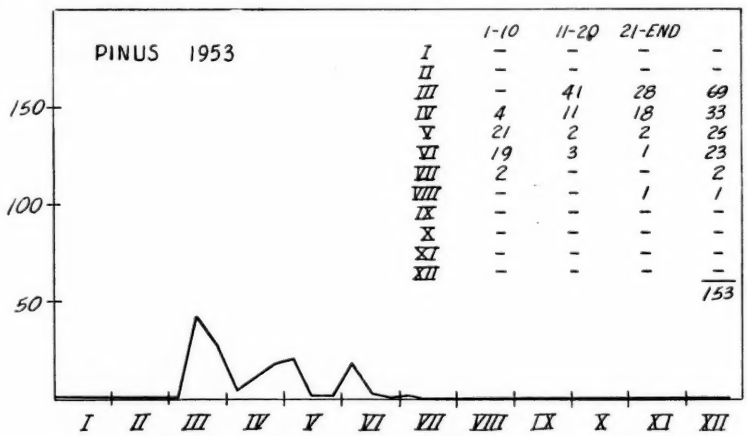

Fig. 1. Incidence of Pine Pollens in the center of Tel Aviv—Jaffa, 1953.

The quantity and the distribution of the rains are the main factors dominating the picture of the pollination. In the year 1953 the quantity was on a normal average, yet the distribution was unequal, with a maximum in the beginning and in the end of the rainy season.

The heavy rains in March and in the first days of April delayed the pollination of *Pinus* as far as to the middle of March and created a wide spread and low curve similar to that of 1952 with a low total number (153).

The pollination of grasses started two weeks later than in the previous years, the peak falls only in the last days of April and the total number is substantially reduced (215 against 642 in 1952). An autumnal pollination of *Gramineae* was just indicated in September and October on the slides exposed in the town; it was very distinct on the slides exposed for comparison in an agricultural region in the north of the country (31 pol-

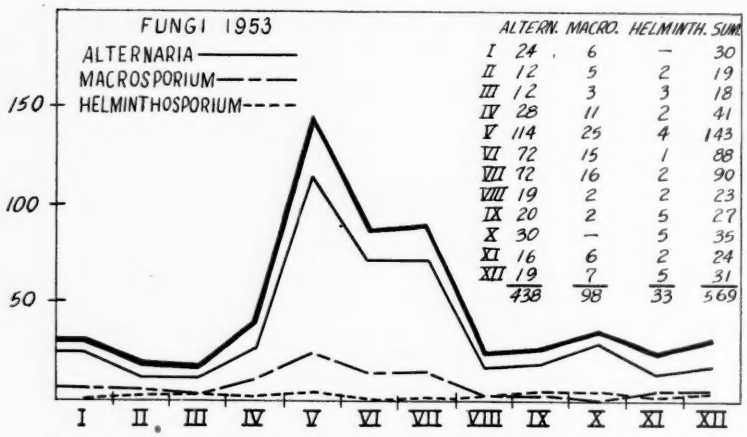

Fig. 2. Incidence of Grass Pollens in the center of Tel Aviv—Jaffa, 1953.

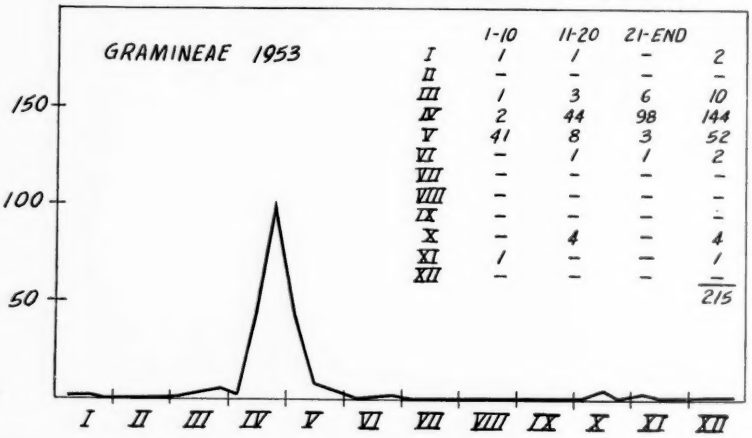

Fig. 3. Atmospheric incidence of macrocomiolia of fungi in Tel Aviv—Jaffa, 1953.

len in an area of 18 x 18 mm in forty-eight hours).

The curves for mold spores, for *Alternaria Macrosporium* and *Helminthosporium* are remarkably similar in the three years of observation, with a sharp rise in May and a lesser one in autumn. The total numbers are quite identical with those of 1952. *Hormodendrum* was on the slides in nearly all the months, abundantly in May, July and August. *Fusarium* was sporadically found.

Smuts were on the slides in all the months of the year, single spores and in small groups. Rusts appeared very abundantly, singles, in groups and often in big heaps in nearly all the months, with a maximal incidence in April and November.

11 Weisel Street

HYDROCORTISONE TREATMENT OF POLLINOSIS

Preliminary Report

MACK V. TRAYNOR, Jr., M.D., LOWELL L. HENDERSON, M.D., LOUIS E. PRICKMAN, M.D., GILES A. KOELSCHE, M.D., HADDON M. CARRYER, M.D., and GUSTAVUS A. PETERS, M.D.

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THE BENEFICIAL effect of cortisone in the treatment of hay fever reported by Carryer and associates[1] in 1950 has been well substantiated. When an adequate supply of hydrocortisone became available shortly before the 1953 ragweed pollen season, it seemed desirable to investigate the effect of that preparation on pollinosis. The purpose of this report is to present the results in thirteen cases of hay fever which were treated in this way.

Patients were selected by the same criteria we had set up for cortisone therapy,[2] namely, severe symptoms despite the usual therapeutic measures, and absence of conditions contraindicating hormone treatment. These included tuberculosis, peptic ulcer, diabetes mellitus, hypertension, congestive heart failure or psychic disturbance.

All thirteen patients had suffered from ragweed hay fever for two to thirty years, and seven had experienced seasonal asthma. Nine were currently receiving injections for desensitization and two others had previously discontinued such treatment for lack of improvement. The symptoms of all were severe enough to make them feel ill, and to impair their working efficiency.

The preparation used for treatment consisted of tablets of hydrocortisone (cortef*) for oral administration, the total daily dose being given in divided amounts at intervals of six or eight hours. Treatment periods ranged from two to twenty-six days, and all coincided with significantly high pollen counts. The total daily dose of hydrocortisone given to each patient, the ragweed pollen count for the respective days and the degree of relief obtained are shown in Table I.

Every patient obtained definite relief from the symptoms of pollinosis, usually within forty-eight hours after administration of hydrocortisone was begun; this held true even during the height of the pollen season. In no case was improvement limited enough to warrant its designation as "fair."

Eight patients whose initial daily doses ranged from 30 to 160 mg. estimated that they were from 50 to 75 per cent improved. This improvement we have designated as "good." In general, this meant that they were able

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Drs. Henderson, Prickman, Koelsche, Carryer, and Peters are from the Section of Medicine, Mayo Clinic and Mayo Foundation.

*The hydrocortisone employed for this study was supplied by courtesy of the Upjohn Company.

TABLE I. TOTAL DAILY DOSE OF HYDROCORTISONE AND DEGREE OF IMPROVEMENT IN EACH CASE, CORRELATED WITH THE DAILY RAGWEED POLLEN COUNT

Date, 1953	Pollen Count*	Total Daily Dose of Hydrocortisone in Milligrams in Cases:												
		1	2	3	4	5	6	7	8	9	10	11	12	13
Aug.														
20	58	40												
21	94	40												
22	230	40												
23	202	40	80											
24	871	40	80											
25	900	80	80											
26	914	80	60	80										
27	1253	80	60	80	80	80	30							
28	835	80	60	80	40	80	30	80						
29	605	80	40	80	80	80	30	80	80	80	90	40		
30	367	80	40	30	40	80	30	80	80	80	90	40		
31	641	80	40	30		80	30	80		80	60	40	90	
Sept.														
1	360	80	40	30	20	60	30			80	60	40	90	160
2	684	80	40	30		40	30			80	60	80	60	160
3	130		40	30		20	30			60	60	80	60	160
4	151		40	30			30			40	30	80	60	160
5	101		40	30			30			20	30	80		
6	94		40	30			30				30	80		
7	65		40	30			30				30	80		
8	72			30			30				30	80		
9	25										30	80†		
Results		Good	Excellent	Good	Good	Excellent	Good	Good	Excellent	Excellent	Excellent	Good	Good	Good

*Granules per cubic yard per twenty four hours.
†Continued for total of twenty six days because of persistent asthma.

to resume their normal activities with no more than moderate discomfort, and their lassitude diminished. The two patients who first received 40 mg. improved further when the dose was later raised to 80 mg. a day. Five patients, who received 80 or 90 mg. initially, reported excellent results, better than 75 per cent improvement, in that symptoms practically disappeared or were minimal. The results for each initial dosage are summarized in Table II.

TABLE II. DEGREE OF RELIEF OBTAINED WITH EACH INITIAL DOSAGE

Initial Daily Dose in Mg.	Results, Cases	
	Good	Excellent
30	1	
40	2	
80	3	4
90	1	1
160	1	
Total	8	5

The degree of relief experienced tended to persist even though the dose was subsequently reduced to a maintenance level or stopped entirely. In regard to the latter, five patients received treatment for five days or less, and none reported any significant increase of symptoms after termination of treatment.

All of the patients with asthma experienced definite relief from the symptoms of that disease, although it tended to recur when treatment with the drug was stopped. Administration was continued for twenty-six days in Case 11 (Table I) for this reason, although the symptoms of pollinosis had subsided promptly.

Essentially no untoward reactions were observed. Two patients who had an unpleasant degree of stimulation from cortisone during the preceding ragweed seasons obtained greater relief from hydrocortisone with much less stimulation.

Evaluation of the efficacy of any treatment for pollinosis must take into consideration the usual fluctuation of symptoms with the pollen count. The season had passed its peak before most of the patients studied had begun treatment with hydrocortisone, and the season was not a severe one compared to some previous years. Furthermore the pollen count subsided to a low level within a week or ten days after cessation of treatment. On the other hand, the count was still high at the time relief was obtained. This relief was marked, and occurred in a selected group of patients who had proved refractory to the usual methods of management.

Although the data do not indicate an optimal dosage, it appears that an initial dose of 80 mg. daily would be adequate in most cases, and even half that amount could be expected to afford definite help in some instances. The prolonged relief observed after courses of the drug lasting four or five days may actually have been due to the declining pollen level, but it raises the question as to whether continuation of a maintenance dose is necessary, unless the pollinosis is accompanied by asthma. Another season or two of investigation may settle this point.

Despite these results, we do not consider hormonal therapy the treatment of choice for pollinosis. In the first place, numerous contraindications deny its use to many patients. Secondly, notwithstanding the lack of observable reactions in the present series, certain complications are a potential threat. Finally, hormonal therapy probably represents only another form of symptomatic treatment, exerting no influence on the primary allergic mechanism.

On the basis of the observations presented, and our previous experience with cortisone, the use of such a preparation as hydrocortisone in pollinosis appears justified in certain carefully selected cases, and if given in the amounts suggested, can be expected to produce benefit with a minimal risk of untoward reactions.

REFERENCES

1. Carryer, H. M., Koelsche, G. A., Prickman, L. E., Maytum, C. K., Lake, C. F., and Williams, H. L.: The effect of cortisone on bronchial asthma and hay fever occurring in subjects sensitive to ragweed pollen. J. Allergy, 21:282-287 (July) 1950.
2. Henderson, L. L., Prickman, L. E., Koelsche, G. A., Carryer, H. M., and Peters, G. A.: Diagnosis and management of hay fever. Proc. Staff Meet., Mayo Clin., 28:497-501 (Sept. 9) 1953.

TREATMENT OF ALLERGIC CONDITIONS WITH SUSTAINED RELEASE CHLORPROPHENPYRIDAMINE MALEATE

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BARELY ELEVEN years have passed since Halpern's studies of Antergan[2] ushered the antihistamines into common therapeutic use. In this period, at least sixty antihistaminic compounds[1] have been examined, evaluated, and either adopted or discarded by the medical profession. More than twenty-six of these drugs are currently available for the physician to choose.[5] For nearly all of them, the manufacturers claim the same virtues; high potency and low incidence of side effects. As each of these drugs became available, we have tried to evaluate these claims in our own practice. Invariably, we have faced the same dilemma; if we used a drug that produced superior antihistamine effects, it also produced more frequent and more unpleasant side effects; if we tried to minimize the side effects, we found we could do so only at the expense of the antihistamine effect. With many patients, in fact, we found it impossible to evoke an antihistamine effect at all without simultaneously producing side effects that made the drug unusable. Ample references in the literature[3,4,6] show that these experiences are far from unique. For the allergist today, no less than a decade ago, the problem has remained to find an antihistaminic drug which truly combines the most relief with the least harm.

For the past nine months we have been studying the effect of a new dosage form of an established antihistamine drug on a series of thirty patients with severe allergic symptoms. The preparation, known as Teldrin*, was made available for investigational use in two alternate strengths, containing 8 and 12 mg of chlorprophenpyridamine maleate respectively. The special dosage form, called a Spansule capsule, is designed to release the active ingredient at a slow, continuous rate over a period of approximately ten hours. This sustained drug release is made possible by dividing the dose among approximately 600 small pellets coated with complex digestible substances of varying thickness and composition. The antihistamine is leached from these minute pellets at various rates depending on the type and thickness of the coating. A theoretical comparison between the effect of the sustained release principle and conventional single dose or t.i.d. medication is illustrated graphically in Figure I.

The theoretical advantages of this dosage form could be summarized as follows: (1) reduction of side effects; (2) prevention of pre-dose "breakthrough"; (3) maintenance of an even, prolonged, "optimal" level of medication; (4) convenience.

*The Teldrin Spansule sustained release capsules were supplied for investigational use by Smith, Kline & French Laboratories, Philadelphia, Pa.

The convenience of the dosage form is obvious. It was patently necessary, however, to determine whether the other theoretical advantages would actually materialize under clinical conditions.

The thirty patients selected for this study were known cases suffering

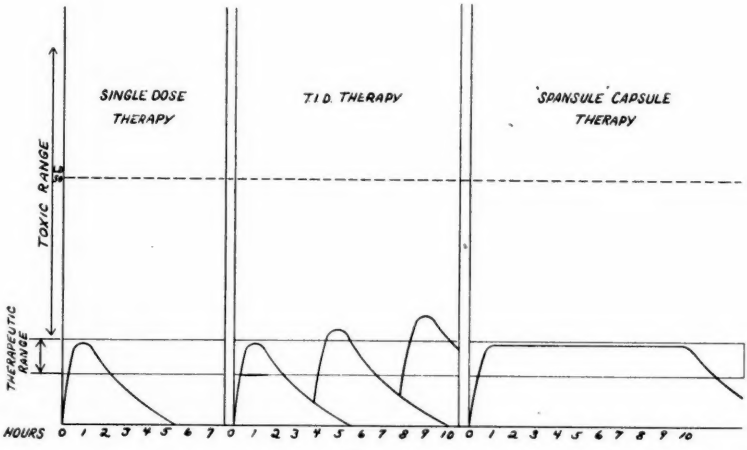

Fig. 1.

from severe allergic symptoms. Nearly all showed marked sensitivities to one or more common allergenic extracts. All but one had previously been treated with one or more antihistamine preparations under similar conditions.

Among these patients, there were eight uncomplicated cases of allergic rhinitis, three of urticaria, and one of eczema. All others presented multiple symptoms in the following frequency: allergic rhinitis, sixteen; asthma, eleven; hay fever, eight; urticaria, five; conjunctivitis, one; cystitis, one; dermatitis, one; tinnitus, one; and angioedema, one. Duration of distress ranged from three months to thirty-six years.

METHOD

In this study the patients were taken fully into our confidence. No placebos were used and the nature of the medication was carefully explained to each patient. Admittedly, this may have created a better psychological effect, but we felt that an honest approach was the one best suited to the treatment of these patients. The intelligence level of this group was relatively high. Most of them were well aware of the advantages and disadvantages of antihistamines and were past the stage of expecting "wonder drugs" to cure them in a single dose. As is common with long-term allergy sufferers, their attitudes tended more toward cynicism than toward the ingenuous belief which predisposes a patient toward a "placebo effect."

TABLE I. A THEORETICAL COMPARISON BETWEEN THE EFFECT OF THE SUSTAINED RELEASE PRINCIPLE AND THE CONVENTIONAL SINGLE DOSE

Patient	Age	Sex	Allergic Conditions	Duration of Distress (yrs.)	Severity of Distress	Sensitivity Reactions	Appearance of Nasal Mucosa	Appearance of Sinuses	Antihistamines Previously Used	Vaccines Given	Response to Teldrin Spansule Capsule Medication		
											Therapeutic Effect	Side Effects	Comments
WW	38	M	Allergic rhinitis, cystitis, hives	6	Severe	House dust, feathers, pyrethrum, coffee, ragweed, lambs quarters, cantaloupe	Pale	Clear	Benadryl, clistin maleate, histadyl, pyribenzamine, thephorin	Dust Vaccine Pollen	Good	Irritated bladder	All other antihistamines irritated bladder also—used ephedrine previously also
AF	42	F	Allergic rhinitis, tinnitus	13	Mod. severe	House dust, feathers, coffee, grapes	Pale	Clear	Many	Dust Vaccine	Good	None	First improvement noted
JH	42	M	Allergic rhinitis	2	Severe	House dust, banana	Pale, polypoid	Clear	Benadryl, clistin maleate, phenergan, pyribenzamine	Dust Vaccine	Excellent	None	Best used
HS	42	F	Allergic rhinitis, hay fever	14	Very severe	Grass, plantain, sheep sorrel, ragweed, lambs quarters, house dust, rice, soybean, willow	Pale, swollen	Clear	Phenergan, thephorin	Pollens Dust Vaccine	Good	None	Required two spansule capsules/day
CL	60	M	Allergic rhinitis, asthma, hay fever	15	Severe	Ragweed, lambs quarters, house dust, orris root, feathers, lima beans	Pale	Frontals dark	Perazil, pyribenzamine	Vaccine Dust	Excellent	None	
WG	43	F	Asthma, urticaria	10	Severe	Chocolate, peppermint, raspberry, blueberry, tomato, tea, oyster, cinnamon, rhubarb, prune, house dust, feathers	Pale	Frontals, ethmoids dark	Perazil, phenergan	Dust Vaccine	Excellent	None	Best ever used
LK	50	M	Allergic rhinitis, hay fever	7	Mod. severe	Oak, house dust, spinach, feathers, kapok	Pale, swollen	Cloudy	Benadryl, histadyl	Dust Vaccine Oak	Good	Sleepy	Prefers benadryl
CR	54	F	Allergic rhinitis	7	Severe	House dust, feathers, banana, grape, tomato	Pale, leaky	Clear	Benadryl, histaclopane, histadyl, perazil, pyribenzamine, thephorin, trimeton	Dust Vaccine	Excellent	None	Best ever used
MJ	51	M	Urticaria	1	Severe	House dust, horse, cocoa, feathers, pyrethrum, tea, spinach, crab, apple, grape, banana	Red	Hazy	Neoantergan	Dust	None	None	

TABLE I. A THEORETICAL COMPARISON BETWEEN THE EFFECT OF THE SUSTAINED RELEASE PRINCIPLE AND THE CONVENTIONAL SINGLE DOSE—CONTINUED

Patient	Age	Sex	Allergic Conditions	Duration of Distress (yrs.)	Severity of Distress	Sensitivity Reactions	Appearance of Nasal Mucosa	Appearance of Sinuses	Antihistamines Previously Used	Vaccines Given	Response to Teldrin Spansule Capsule Medication		
											Therapeutic Effect	Side Effects	Comments
AF	10	M	Allergic rhinitis, asthma, hay fever	9	Severe	Grass, peas, ragweed, house dust	Very pale	Clear	Benadryl, pyribenzamine	Pollen Dust Vaccine	Very good	None	
RB	57	F	Allergic rhinitis, hay fever	5	Severe	Ragweed, house dust, rabbits, feathers, bananas	Pale	Clear	Chlortrimeton pyribenzamine	Pollen Dust	Excellent	None	
EU	39	F	Allergic rhinitis	8	Severe	House dust	Very pale	Clear	Phenergan	Dust	Excellent	None	
JA	14	M	Allergic rhinitis	2	Severe	House dust, chicken	Pale, swollen	Clear	Benadryl	Dust Vaccine	Very good	None	
WB	36	M	Eczema	36	Very severe	House dust, feathers, coffee, beef, clams, peas, spinach, flax, pineapple, brewer's yeast	Normal	Clear	Many	Dust	None	Reddened skin	All antihistimines same effect
RR	28	F	Allergic rhinitis, asthma, hay fever	28	Severe	Grass, ragweed, lambs quarters, house dust, carrot, spinach, alternaria	Pale, polypoid	Clear	Phenergan	Pollen Dust Vaccine	Slight	None	
AH	30	F	Allergic rhinitis, dermatitis	10	Mod. severe	House dust, cantaloupe, banana, cocoa	Pale	Clear	Pyribenzamine	Dust Vaccine	Good	None	
HO	52	M	Allergic rhinitis, asthma, urticaria, angioedema	10	Severe	House dust, pyrethrum, tobacco, coffee, shrimp, cantaloupe, cocoanut, cocoa	Pale	Hazy	Benadryl, histadyl, clistin maleate, phenergan	Dust Pollen Vaccine	Excellent	None	
TB	31	M	Allergic rhinitis	1	Very severe	None	Pale	Clear	Many	Vaccine	Excellent	None	Needs 2/day
CC	27	M	Urticaria	1	Severe	Ragweed, lambs quarters, pyrethrum, coffee, tobacco, house dust, feathers, cocoa, oats, tea, crab	Red	Clear	Histadyl, phenergan	Dust Vaccine	Good	None	
MD	43	F	Allergic rhinitis	10	Severe	House dust, feathers, cabbage	Pale	Hazy	Many	Dust	Excellent	None	
JH	8	M	Allergic rhinitis, asthma, conjunctivitis	6	Very severe	Lambs quarters, dust, potato, orange	Red, blocked	Clear	Benadryl	Dust Vaccine	Excellent	None	

TABLE I. A THEORETICAL COMPARISON BETWEEN THE EFFECT OF THE SUSTAINED RELEASE PRINICPLE AND THE CONVENTIONAL SINGLE DOSE—CONTINUED

Patient	Age	Sex	Allergic Conditions	Duration of Distress (yrs.)	Severity of Distress	Sensitivity Reactions	Appearance of Nasal Mucosa	Appearance of Sinuses	Antihistamines Previously Used	Vaccines Given	Response to Teldrin Spansule Capsule Medication		
											Therapeutic Effect	Side Effects	Comments
MD	33	M	Urticaria	1	Severe	None	Red	Clear	Pyribenzamine	Vaccine	Good	None	
AF	4	M	Allergic rhinitis, asthma, hay fever	2	Severe	Grass, ragweed, house dust, orris root, oats, coffee, tea, grapefruit, alternaria, fusarium	Pale	Clear	Chlortrimeton, phenergan, pyribenzamine	Pollen Dust Molds Vaccine	Excellent	None	Used 8 mg. dosage
BC	46	M	Allergic rhinitis, asthma	9	Severe	House dust, coffee	Pale	Dark	Many	Dust Vaccine	Very good	None	
LI	38	F	Allergic rhinitis	2	Very severe	None	Pale	Clear	Many	Vaccine	None	None	Only relieved by cortone
JR	25	F	Allergic rhinitis	5	Very severe	House dust, feathers	Pale, swollen	Clear	Phenergan	Dust Vaccine	Very good	None	
SW	19	F	Allergic rhinitis, asthma	3	Mod. severe	Dust, cocoa, spinach	Pale	Dark	None	Dust Vaccine	Good	None	
GW	17	F	Allergic rhinitis, rhinitis, asthma hay fever	3	Severe	Ragweed, lambs quarters, cow, house dust, alternaria, orris root, spinach	Red	Clear	Phenergan	Dust pollens, Orris, Alternaria	Good	None	
JK	46	M	Asthma urticaria	¼	Severe	Ragweed, cow, house dust, feathers, onion, baker's yeast	Normal	Clear	Histadyl	Dust Vaccine	Slight	None	
HH	49	M	Allergic rhinitis, asthma, urticaria	"yrs."	Severe	House dust, banana, coca cola, lemon, grapefruit	Pale swollen	Clear	Phenergan	Dust Vaccine	Very good	None	

It seemed obvious that if the Spansule capsule dosage form were to extend the absorption of medication as predicted, any untoward effects would be equally prolonged. Consequently we took particular care to question each patient thoroughly for evidence of previously exhibited antihistamine sensitivity. Those with histories of severe antihistamine reactions were, of course, excluded from the study. On the other hand it would have been pointless to rule out Spansule capsule medication in every case where side effects had been encountered, especially since the possibility that this preparation would reduce these effects was one of the main features to be evaluated.

Pretreatment examinations included complete sensitivity tests and an examination of sinuses and nasal mucosa.

The usual antihistamine dosage we prescribed was one 12 mg Spansule capsule daily. The dosage for two patients who showed only limited responses at this level was increased to two 12 mg Spansule capsules daily. For a third patient, a four-year-old child, the dosage was reduced to one 8 mg Spansule capsule daily. All patients were treated concurrently with one or more anti-allergen extracts and stock catarrhal vaccines chosen in accordance with their specific sensitivities. The patients were studied over a nine-month period. Each patient received the medication for a minimum of six weeks. This, in our experience, has proved an adequate time to evaluate antihistamine medication.

RESULTS

Table I contains the basic data and results obtained for the thirty patients studied. As shown in this table, twenty-five of these patients achieved results that ranged from "good" to "excellent." One patient (A.F.) noted the first relief she had experienced in thirteen years of treatment during which the entire gamut of antihistamines had been tried without success. Each of the three children included in the study obtained very marked relief and none experienced any side effects. As noted, we used the 8 mg Spansule capsule with one four-year-old child (A.F.), but the other two children, aged eight and ten respectively, seemed quite able to tolerate the full 12 mg dosage.

Results, of course, were not uniformly excellent. Two patients achieved only slight relief and three obtained no relief at all. It is significant, however, that for each of these patients all previously used antihistamines had proved equally ineffectual. Included in this group were a severe life-long case of eczema and a very severe case of allergic rhinitis with no demonstrable sensitivities who responded only to Cortisone. The incidence of side effects—three cases—was considerably less than usual in our experience. Not one of these patients had failed to show side reactions to all other antihistamines. Moreover, with two of these patients—despite these side effects—the over-all results were adjudged "good." This classification seemed amply justified when the degree of relief from the severe discom-

fort of allergic symptoms was weighed against the relatively mild discomfort attributable to the medication.

DISCUSSION

Although these results are not unanimous, they are, in our opinion, remarkably good. We feel, after a careful study covering the entire range of antihistamine medication, that they are unquestionably the best we have encountered. In only one case (L.K.) did a patient report better relief from a previously used antihistamine. For the majority, the results were quite the reverse and several patients volunteered opinions that this drug was the best they had ever tried.

We have evaluated the basic drug—chlorprophenpyridamine maleate—in tablet form over a sufficiently long period of time to thoroughly appraise its usefulness. In this form it is a fairly satisfactory antihistamine but without question the use of this same drug in Spansule capsule form has given notably better results. It is our feeling, therefore, that the Spansule capsule method, rather than the fundamental drug, is the important factor in these superior results. We feel that release of the drug in smaller amounts over a ten to twelve hour period has demonstrably reduced both the incidence and the severity of the side effects which we have usually encountered when the drug is given in a single tablet. It has done so, moreover, without reducing the antihistaminic efficacy of the basic drug.

SUMMARY

1. A series of thirty patients suffering with severe allergic manifestations due to multiple sensitivities were treated with chlorprophenpyridamine maleate in a sustained release dosage form known as Teldrin Spansule capsules.

2. Results obtained with this group were as follows: excellent, eleven; very good, five; good, nine; slight, two; none, three.

3. Limited side effects were encountered with three patients. They consisted of one case each of sleepiness, bladder irritation, and reddening of the skin.

4. The prolonged release of medication provided by this Spansule capsule dosage form produced significantly better results than we have experienced using the same drug in tablet form.

5. It is our belief that this drug used in this form provides the best method available for antihistamine medication.

REFERENCES

1. Brown, E. A., and Krabek, W.: Antihistaminic Agents. Ann. Allergy, 8:571-575 (July-Aug.) 1950.
2. Halpern, B. N.: Les antihistaminiques de synthese. Essais de chimiotherapie des etats allergiques. Arch. Internat. Pharmacodynamie 68:339-408, 1942.
3. Hansel, F. K.: Clinical Allergy. St. Louis, C. V. Mosby Co., p. 712, 1953.
4. Leblond, S.: Antihistaminic drugs. Canad. M.A.J., 63:275 (Sept.) 1950.
5. Modern Drug Encyclopedia & Therapeutic Index. New York, Drug Pub., Inc., 5: 1952.
6. Reicher, J., and Schwartz, E.: The symptomatic treatment of allergic diseases with Chlortrimeton. N. Y. State J. Med., 50:1383 (June) 1950.

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ONE YEAR'S EXPERIENCE WITH SUSTAINED RELEASE ANTIHISTAMINE MEDICATION

An Experimental and Clinical Study

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COMMON FAULTS of currently available antihistamines are their short duration of action and their side effects, especially drowsiness. Past attempts to circumvent these shortcomings largely centered about synthesizing new compounds. As a result, the antihistaminic field, apparently bound only by the limits of organic chemistry, is now already overcrowded with numerous agents possessing little or no appreciable difference in their over-all clinical usefulness.

An approach which appears promising for significantly increasing the duration of antihistaminic activity, without further increasing the number of antihistamines, is that of incorporating clinically established antihistamines in such dosage forms as timed disintegration tablets, delayed action tablets, and sustained release capsules.

Last year I obtained for investigational use, the antihistamine chlorprophenpyridamine maleate, so prepared in a new oral dosage form that its resultant therapeutic effect was designed to last approximately twelve hours following the administration of a single oral dose. This form, called sustained release antihistaminic medication consists of a capsule containing three average doses of the antihistamine, a total of 12 mg, distributed among 600 tiny pellets. Some of the pellets are uncoated; others are coated with varying thicknesses of a digestible substance. When ingested, the uncoated pellets are designed to release approximately 3 to 4 mg of chlorprophenpyridamine for absorption as soon as the capsule dissolves. Later, the coated antihistaminic pellets, because they are overlayed with varying thicknesses of a digestible film, are designed to release gradually and continuously the remainder of the drug to sustain its initial therapeutic effect. Figure 1 schematically compares the response expected from giving an antihistamine in sustained release form with that from giving it intermittently in conventional form, that is, tablets or capsules, three times daily. As shown in Figure 1, one might, hopefully, expect that side effects, since they seem related to peaks of drug absorption, could be reduced through the even release of medication afforded by this new pharmaceutical form.

These hypothetical features remained to be tested; consequently we undertook to assess the long-acting property and side effects of sustained release antihistaminic capsules. Inasmuch as Tislow,[6] Silbert,[5] and others[1,2,4] have already demonstrated the clinical efficacy and relative low

Presented at the Decennial Congress of the American College of Allergists, Miami Beach, Florida, April 7, 1954.

toxicity of chlorprophenpyridamine, the investigation of this antihistamine prepared for sustained release concerns efficiency of the form rather than efficacy of the drug.

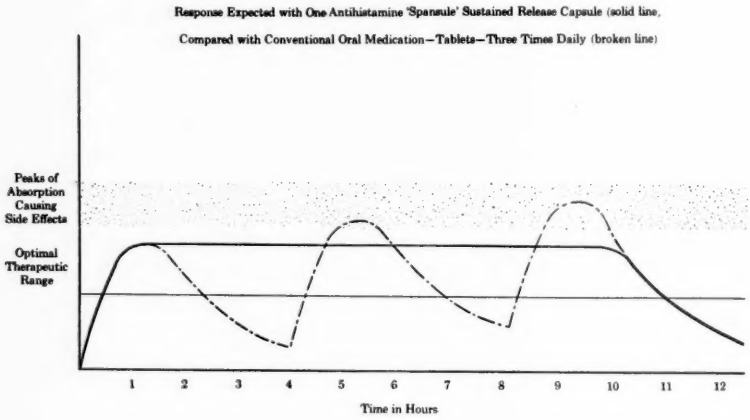

Fig. 1

EXPERIMENTAL

As a prelude to clinical work, liberation of drug from the sustained release preparation was checked by measuring rate of release in artificial gastric and intestinal juice using a modification of the U.S.P. tablet disintegration apparatus. In it, pellets containing the antihistamine prepared for sustained release and emptied from their capsules, were raised and lowered into the juice by means of a basket-rack assembly; at intervals during the test, samples of the preparation were removed and assayed. The results of these *in vitro* studies, given in Figure 2, show that the drug is gradually and continuously released over a course of approximately six to eight hours.[3] Considering the fact that, in humans, the action of a drug, after its release, will persist until it is inactivated or excreted, it appears that this preparation should produce an effect that lasts ten hours or more.

Securing data on antihistamine blood levels in animals proved fraught with difficulties, consequently, onset and duration of action *in vivo* could only be estimated. This was done by administering large doses of chlorprophenpyridamine maleate, prepared for sustained release, to dogs and observing the animals for such physiologic effects as dry mouth, dilated pupils with sluggish response to bright light, alertness, tenseness, and slight head movements. These signs, characteristic of this antihistamine when given to dogs in large doses, occurred within twenty to forty minutes following administration of the drug, and persisted for more than ten hours.[3]

TABLE I. DIAMETER OF WHEAL RESULTING FROM HISTAMINE PHOSPHATE* INJECTED INTRADERMALLY IN FLEXOR SURFACE OF FOREARM
Readings, Expressed as Centimeters, Were Made Fifteen Minutes After Each Injection

Subject	Control	Time				
		2 Hours	4 Hours	6 Hours	8 Hours	10 Hours
M. R.	1.70	1.50	1.50	1.50	1.25	1.20
M. P.	2.00	2.50	1.50	1.00	1.50	1.50
L. C.	2.00	1.50	1.50	1.50	1.00	1.25
H. H.	2.50	1.25	1.00	1.00	1.00	—

*0.1 cc. H.P.(1:10,000).

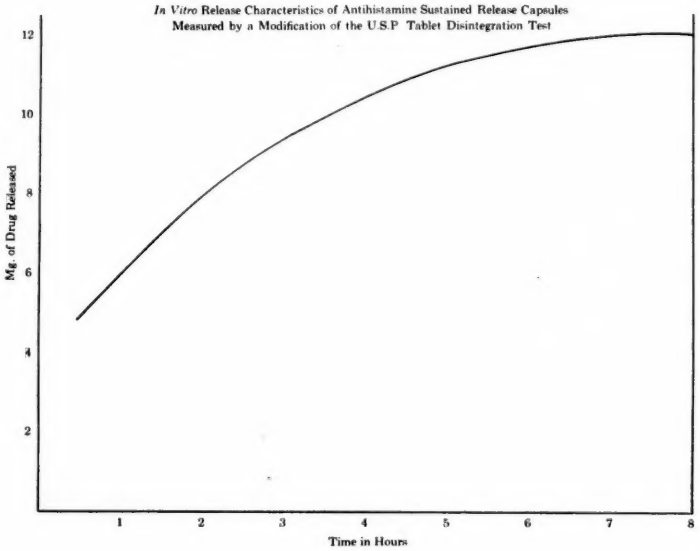

Fig. 2

In view of the unsuccessful efforts to measure antihistamine blood levels in animals, no attempt was made to obtain such levels in humans. Instead, two techniques were employed as a means of determining whether the long-acting properties of the preparation could be demonstrated in humans; serial kodachromes were taken of patient response to intradermal histamine-neutralization tests and serial radiograms were taken of patients who had been given the drug containing a radiopaque substance.

Table I summarizes the results of our intradermal tests. From previous experience, we know that because of many uncontrollable factors, data derived from intradermal tests are often subject to slight variations In our series, 0.1 cc. of 1:10,000 aqueous solution of histamine phosphate was injected into the flexor surface of the forearm of each of four subjects. Diameter of the resultant wheal was measured ten to fifteen minutes later.

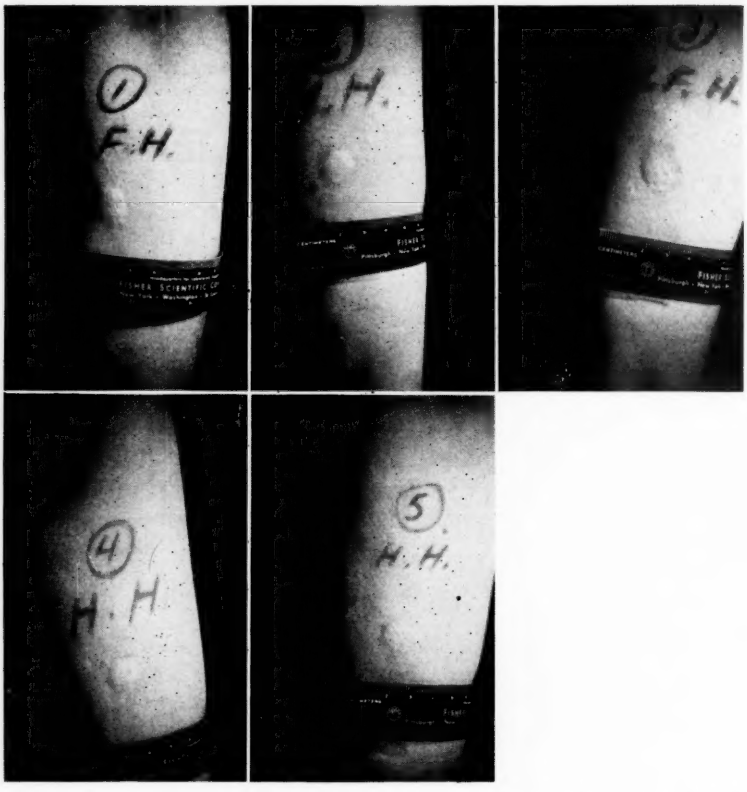

Fig. 3. Representative histamine neutralization response of subject to sustained-release antihistamine.

One sustained release antihistaminic capsule was then administered orally. At two hour intervals, over a course of ten hours, the injections were repeated as before. The response of subject H. H., typical of this series, is shown in Figure 3. In general, there was a diminution of wheal size, a reduction of zone of erythema, and less itching, for a ten-hour period, following administration of the sustained release antihistaminic capsules.

Roentgen tracings following the course of the medication through the gastrointestinal tract, by means of an incorporated radiopaque material, showed that rate of drug release in humans parallels that determined *in vitro*. Figure 4, summarizing our results in three non-fasting patients given this material, shows that the antihistamine is gradually and continually released over a period of seven hours or more, depending on gastrointestinal motility.

The results shown in Figure 5 are, for the most part, representative of

those observed in this series. The first plate shows the number of pellets present one-half hour after this subject ingested a sustained release capsule containing radiopaque material; the second plate shows the number of pellets present in the same subject after one hour; the third plate, after

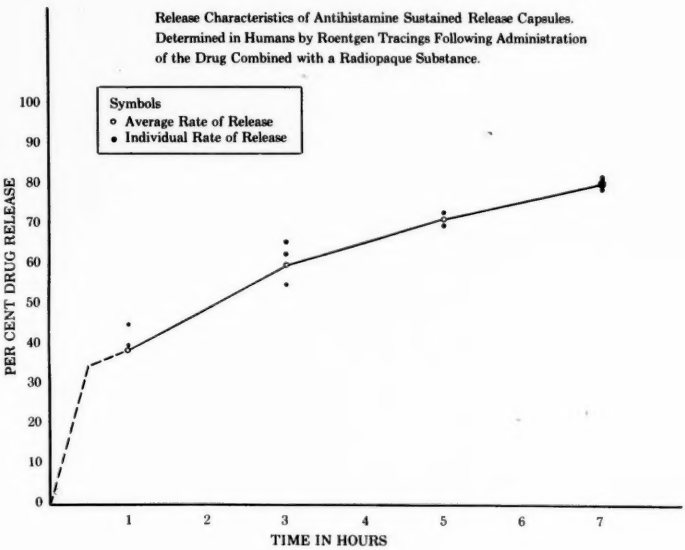

Fig. 4

three hours; the fourth, after five hours; and the fifth, after seven hours. (When these plates are viewed with a viewing box, the pellets can clearly be seen, but for photographic reproduction the plates have been treated to increase the visibility of the pellets.) In preliminary work, it developed that measuring levels of radiopaque material in the saliva yielded equivocal results because the radiopaque material was recycled each time the patient swallowed.

CLINICAL

During the past year, sustained release antihistaminic capsules were administered to 357 patients seen in private practice and clinical work at Columbia Hospital, Pittsburgh, Pennsylvania. Table II summarizes the clinical characteristics and age distribution in this series. The group—156 men and 201 women—ranging in age from eleven months to seventy-six years, consisted of patients suffering from seasonal and perennial hay fever, bronchial asthma complicated by other allergic manifestations, allergic rhinitis, allergic dermatoses, and, to a lesser extent, allergic conjunctivitis, allergic headaches, and pruritus due to various etiologies. Pa-

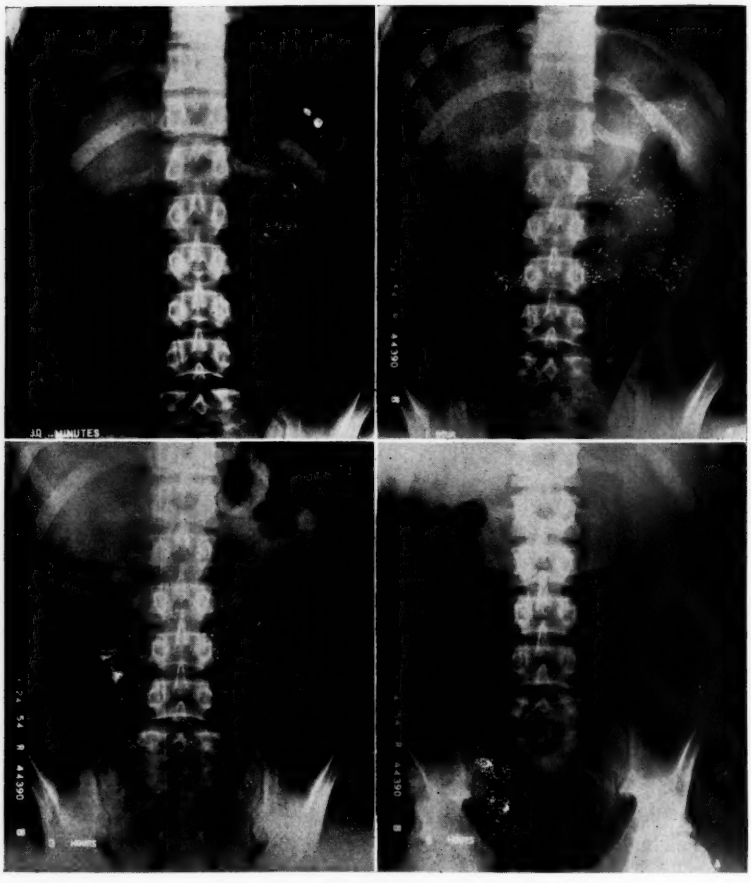

Fig. 5. Plates showing number of pellets present one-half hour after subject ingested a sustained release capsule containing radiopaque material, number of pellets present in the same subject after one hour, number of pellets present after three hours, and number of pellets after five hours.

tients were unselected except that we tried to choose those who showed promise of co-operation and some ability of self observation.

At least four study plans were considered, but later abandoned. As yet, there appears to be no satisfactory means for objectively evaluating antihistamines in practice. Using such controls as placebos, another antihistamine, or the patient's response to previous antihistaminic therapy often gives impressive but invalid results. Patient individual susceptibility to allergens, variable patient response to different anthistamines, variable circumstances as changing pollen count, rainfall, humidity, environment

TABLE II. CLINICAL CHARACTERISTICS AND AGE DISTRIBUTION

Diagnoses	Number of Patients	1-9*	10-19	20-29	30-39	40-49	50-59	60-69	70 & Over
Hay fever	137	9	43	33	23	16	9	4	0
Bronchial asthma	70	10	13	5	11	9	11	9	2
Allergic rhinitis	73	2	9	10	15	15	13	8	1
Allergic dermatoses	53	9	5	13	7	6	8	4	1
Allergic conjunctivitis	9	3	0	1	3	1	0	1	0
Allergic headaches	10	0	0	3	3	2	1	1	0
Pruritus	5	2	0	0	1	2	0	0	0
Totals	357	35	70	65	63	51	42	27	4

*Includes one patient who was eleven months old.

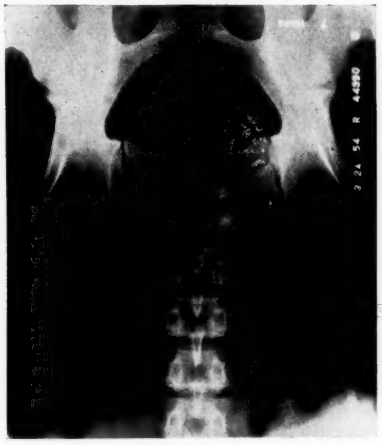

Fig. 6. Number of pellets present after seven hours.

(especially in this era of home and office air-conditioning) present a formidable barrier to controlled studies. Studies designed to balance these variables in which appropriate controls are used are, of course, to be encouraged.

One consistent means we all use in evaluating antihistamines and other medications, though it may sound unscientific, is a reliance on our patients' comments as to whether the effect of a prescribed drug has been beneficial. Our plan, therefore, was based on this common practice, and, though quite simple, is subject to the usual shortcomings. Each patient was given a packet containing a supply of sustained release antihistaminic capsules* with directions to take two a day: one in the morning, and one in the evening. Children were told to take one capsule daily, and if necessary, a second capsule, depending on their response. Those who experienced dif-

*Supplied for investigational use as Teldrin Spansule capsules by Smith, Kline and French Laboratories, Philadelphia, Pa.

TABLE III. CLINICAL RESULTS WITH SUSTAINED RELEASE ANTIHISTAMINIC CAPSULES

Diagnoses	Excellent	Good	Fair	None
Hay fever				
Ragweed	72	18	9	3
Grass	16	4	4	0
Ragweed-grass	7	2	2	0
Bronchial asthma: *(with)*				
Ragweed H.F.	20	7	4	1
Sinusitis	7	1	2	1
Other Etiologies	12	5	5	5
Allergic rhinitis: *(with)*				
Ragweed-grass H.F.	11	1	1	2
Sinusitis	4	0	1	0
Other Etiologies	39	6	3	5
Allergic dermatoses				
Urticaria	15	4	4	3
Eczema	8	2	0	0
Dermatitis	11	4	2	0
Allergic conjunctivitis	5	2	1	1
Allergic headaches	5	2	2	1
Pruritus	4	0	0	1
Totals	236	58	40	23

ficulty in swallowing capsules were given the contents of the capsule in fruit juice.

Each was told that we would later like his opinion as to the acceptability of this antihistaminic preparation. Parents were asked to judge the results in the children. Inasmuch as most of these patients had a long history of allergies and had been exposed to a gamut of antihistamines, we felt that their comments would be tempered by past experience and, hence, could be fairly well relied upon. Duration of treatment with this antihistaminic preparation ranged from one week to one year; however, all patients took the medication for at least one week. Those who benefited during the first week of treatment were given additional supplies of sustained release capsules and asked to continue this therapy so that we could determine whether the resultant symptomatic relief was attributable to the medication. The vast majority of patients, given the sustained release antihistamine as adjuvant therapy, continued to receive specific hyposensitization.

RESULTS

Tables III and IV, respectively, show the symptomatic results and side effects obtained in this group of 357 patients. Degree of relief was graded as "none," "fair," "good" and "excellent." "None" means that the preparation afforded slight to no appreciable benefit. If the patient reported some relief, such as less sneezing or reduced nasal discharge, his response was graded "fair." When symptoms could be controlled to the extent that, though still present, the patient no longer minded them, the response was considered "good." It was considered "excellent" when the patient was essentially free of symptoms. As we know, patients whose allergy is stubborn to the extent that they consult an allergist seldom obtain complete symptomatic relief with antihistamines.

TABLE IV. INCIDENCE OF SIDE EFFECTS WITH SUSTAINED RELEASE ANTIHISTAMINIC CAPSULES*

Diagnoses	Number of Patients	Drowsiness			Headache	Dry Mouth
		Mild	Moderate	Severe		
Hay fever	137	7	4	3	—	—
Bronchial asthma	70	3	4	2	—	1
Allergic rhinitis	73	3	5	2	2	1
Allergic dermatoses	53	1	2	0	1	—
Allergic conjunctivitis	9	—	—	—	—	—
Allergic headaches	10	—	—	—	—	—
Pruritus	5	—	—	—	—	—
Totals	357	14	15	7	3	2

*Nausea, which occurred in one patient, subsided even though she continued the medication. One reported insomnia; one, nervousness; one child experienced diarrhea.

As shown in Table III, 66 per cent of the group reported excellent symptomatic relief of allergic distress with sustained release antihistaminic capsules. Sixteen per cent obtained good relief; 11 per cent, fair relief; 7 per cent obtained questionable or no relief. Individual patient response varied, but, in general, the sustained release capsule provided relief within one-half to one hour after its administration, and that relief, as estimated by the patients, lasted as long as ten to twelve hours. In some children, the duration of effect exceeded twelve hours.

One patient who had been accustomed to taking four to five antihistaminic tablets daily disregarded our "two capsules a day" directions and took four to five sustained release antihistaminic capsules daily for one week. This woman, despite the fact that she had taken four to five times the average daily dose of this drug, experienced no side effects. Whether this accident demonstrates that this new pharmaceutical form provides a gradual, continuous release of medication is open to conjecture; however, it seems unlikely that the patient could have tolerated this dosage without being sedated unless the drug had been protractedly released.

The incidence of side effects with sustained release antihistaminic capsules was unusually light; only forty-one of 357 reported side effects (12 per cent). Drowsiness, occurring in thirty-six patients, was the most prominent side effect. In almost half of this group, drowsiness was mild. Children given one or two sustained release antihistaminic capsules daily tolerated the medication very well. In only three of thirty-five patients under ten years were side effects noted, two were made drowsy, one had diarrhea, which subsided when he discontinued the drug.

DISCUSSION

The results of this investigation confirm the postulated long-acting property and low side effect liability of sustained release antihistaminic capsules. A dosage of two capsules daily—one in the morning and one in the evening—proved effective, as adjuvant therapy, in relieving symptoms of hay fever, allergic rhinitis, and allergic dermatoses. Use of the

preparation in allergic conjunctivitis, allergic headaches, and pruritus shows promise; however, the number of patients with these conditions in this series, 9, 10, and 5 respectively, is insufficient for discussion. Several patients with asthma complicated by other allergies contended that their wheezing had been reduced since taking the capsules.

Sustained release antihistaminic capsules, aside from their long-acting property and low incidence of side effects, provide an obvious advantage of patient acceptance. From the standpoint of convenience, they were heartily endorsed by nearly all patients. Perhaps those who commented that this preparation provided superior relief to other antihistamines had allowed their opinions on efficacy to be influenced by its requiring less frequent administration. Except for drowsiness in 10 per cent of the patients, side effects with sustained release antihistaminic capsules were practically nil.

SUMMARY

This investigation was undertaken to evaluate the long-acting properties of sustained release antihistaminic capsules, a new oral dosage form that is designed to provide an antihistaminic effect that lasts twelve hours following a single oral dose.

In vitro release data, measured by a modification of the U.S.P. tablet disintegration test, which showed that the drug was gradually and continuously released over a period of eight hours, were corroborated by *in vivo* studies in dogs. Protracted drug release, which lasted approximately ten hours, was demonstrated in humans by serial kodachromes recording results of intradermal histamine neutralization reactions, and by serial roentgen tracings following the course, through the gastrointestinal tract, of the antihistamine containing a radiopaque compound.

Symptoms of allergic distress were treated in 357 patients to assess the clinical efficiency of sustained release antihistaminic capsules. Sixty-six per cent of the group obtained excellent symptomatic relief; 16 per cent obtained good relief; 11 per cent, fair relief; 7 per cent obtained no relief. The preparation proved effective in relieving symptoms of hay fever, allergic dermatoses, allergic conjunctivitis, and various pruritic conditions. Allergic reactions superimposed on bronchial asthmatic conditions responded, but, asthma, for the most part, was unchanged. Side effects, an incidence of 12 per cent, consisted of drowsiness, dryness of the mouth, headache, insomnia, and nervousness. The incidence of drowsiness, the most prominent side effect, was 10 per cent.

ACKNOWLEDGMENT

Special thanks are due Dr. William J. McGregor and Dr. J. H. Vastine for preparing the roentgen tracings, and Dr. Earl Vandegrift for taking the kodachromes. I am also indebted to Dorothy Betts, R.N., Director of Out-Patient Clinic, Columbia Hospital, Pittsburgh, Pa., for her fine co-operation and to the hospital personnel who served as subjects.

REFERENCES

1. Fond, I. A.: A comparative study of effects of certain antihistamines on skin reactivity. Annals of Allergy, 10:449-453, 1952.
2. Gaillard, G. E.: Clinical Experience with Chlor-Trimeton in Hay Fever and Other Allergies. Ann. Allergy, 8:318-321, 1950.
3. Personal Communication, Dr. R. T. Conner, Smith, Kline & French Labs., Philadelphia, Pa.
4. Seidmon, E. E. P.: Treatment of Hypersensitive Rhinitis and Other Allergic Diseases with Chlor-Trimeton. Annals of Allergy, 9:387-389, 1951.
5. Silbert, N. E.: Evaluation of Chlor-Trimeton Maleate in hay fever and a variety of allergic diseases. New England J. Med., 242:931-932, 1952.
6. Tislow, R., Labelle, A., Makovsky, A. J., Reed, M. A. G., Cunningham, M. D., Emele, J. F., Grandage A., and Roggenhofer, R. J.: Pharmacological evaluation of Trimeton, 1-Phenyl-1-(2-pyridyl)-3-N,N-Dimethylpropylamine, and Chlor-Trimeton, 1-(p-chlorphenyl)-1-(2-pyridyl)-3-N,N-Dimethylprophylamine. Federation Proc., 8:338, 1949.

6111 Jenkins Arcade

POLLEN SURVEYS

(Continued from Page 260)

Erdtman's book on the angiosperms, entitled "Pollen Morphology and Plant Taxonomy." This book was published in Sweden and is written by an expert in paleopalynology. The illustrations are those of fossil pollen grains rather than of fresh pollen grains such as we deal with in allergy.

The sampling instrument mentioned is available through the Wilkins-Anderson Company of Chicago, or Dr. Durham will send you a working drawing from which you can have a mechanic build one according to specifications.

Dr. Grafton Tyler Brown's monograph on "Pollen Slide Studies" (Charles C Thomas) clearly states that the researcher with no previous botanical training but who can read and use a microscope can learn how to do reliable pollen counts from the information contained in this manual. The book also helps in verifying the identity and purity of dry pollens to be used for the preparation of diagnostic and treatment extracts. There are many separate drawings of pollen grains and fungus spores, as well as thirty-four photomicrographs. Illustrations of pollen traps, methods of slide counting, a new type of pollen-slide shelter, and methods of making a pollen slide study, with detailed studies of pollen grains, are also very helpful. Drawings of the common fungus spores, including rusts and smuts, are included. An excellent reference list is also appended for those interested in making pollen studies in their own particular areas.

An excellent example of the work of an area pollen survey committee is contained in a very thorough monograph produced by the Maine Air-Borne Pollen and Fungous Spore Survey composed of Fay Hyland, B. F. Graham, Jr., F. H. Steinmetz, and Martyn Vickers, published by the University of Maine in July, 1953. Fay Hyland is a professor of botany, B. F. Graham, Jr., a former instructor in botany, F. H. Steinmetz is professor of botany and head of the Department of Botany and Entomology, and Martyn A. Vickers, M.D., was director of the survey. Following the passage of the necessary legislation, the Department of Botany and Entomology of the University of Maine was authorized to conduct the survey, of which Dr. Vickers was named director. Every allergist should have a copy of this survey whether he is going to send patients to Maine or not. The plates showing atmospheric pollen are from Roger P. Wodehouse's *Aerobiology*, Publication No. 17 of the American Association for the Advancement of Science, 1942. A chart showing pollen seasons is through the courtesy of Abbott Laboratories. There is a complete summary of pollen and fungous spore incidence in Maine in 1950 and 1951, also condensed to show incidence in twenty-five areas in Maine.

CLINICAL EVALUATION OF A NEW ANTIHISTAMINE DRUG, FC-1

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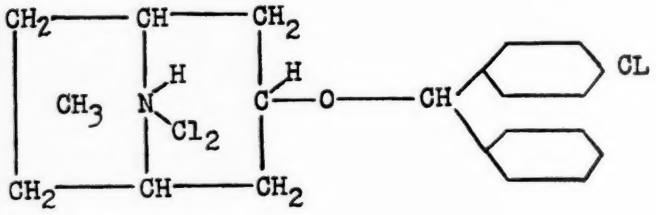
THIS STUDY involves a survey of a new antihistamine, FC-1, having the chemical formula, Tropine-4-chlorobenzhydryl ether hydrochloride.



$C_{21}H_{25}ONCl_2$ M= 378

The above is the structural formula of this compound. The molecular weight is 378. The product is a white crystalline non-hygroscopic compound which is stable and has a melting point of 215-219°C. It is readily soluble in water as well as some other organic solvents. The base forms a crystalline picrate melting at 85° C.

It will be noted that the tropine nucleus (the left-hand portion of the formula) makes this compound quite similar to atropine.

This compound is not closely related to any antihistamine medication in general use. Because the effective dose of this drug has been found in preliminary trials to be 5 mg or less per day and the toxicity studies revealed the MLD 50 to 117 mg/kg of body weight, this antihistamine substance was thought to be quite safe for human use. In laboratory tests, it was demonstrated that when administered to animals, this compound conferred much longer protection against the effects of histamine than did other presently used agents. This led us to believe that the antihistaminic effects in humans would be more prolonged than some of the other available histamine antagonists and that the toxicity would be exceptionally low.

Drs. Kaplan and Aaronson are from the Chicago Medical School; the Allergy Clinics, Mount Sinai Hospital, Chicago, Illinois, and the Mount Sinai Research Foundation.

The drug was supplied and this study was supported, in part, by a grant from the Schenley Corporation.

The toxicity studies revealed that the LD-50 values were determined arithmetically and are as follows:

Oral LD-50 = 105 mg/kg
Intravenous LD-50 = 20 mg/kg
Intraperitoneal LD-50 = 41 mg/kg

This compares very favorably with toxicity studies of other well known antihistamines.

Schenley Laboratory data would indicate that Compound FC-1 when given in a dose of 1 mg/guinea pig, intraperitoneally, is at least as effective an antihistaminic as Pyribenzamine. When the dose was increased to 5 or 10 mg/guinea pig, the antihistamine effect of Compound FC-1 lasted much longer than that of Pyribenzamine.

Compound FC-1 also appeared to be less toxic than Pyribenzamine in guinea pigs. At the dose level of 10 mg/animal, Pyribenzamine is definitely toxic to guinea pigs (some were killed by this dose in previous experiments), whereas the same dose of Compound FC-1 is apparently non-toxic.

The above data indicates that the antihistaminic effect of Compound FC-1 in guinea pigs lasts about three times as long as that of Chlortrimeton and about fifteen times as long as that of Pyribenzamine.

The experimental period was primarily that of the Chicago area 1953 ragweed pollinating season. However, many of the patients were carried for longer periods, corresponding to the local grass and mold seasons. Also included were patients who, in addition to seasonal allergic rhinitis, have perennial allergic rhinitis, with or without other allergic manifestations. Aside from the above, the group was unselected as to age, race, sex, or social status. All patients included were ragweed pollen sensitive by skin test and clinical symptoms. Most patients had received other antihistamine drugs prior to the time of this study. In addition to receiving specific hyposensitization therapy, and FC-1, those requiring additional therapy received other medication as needed for comfort. The ages ranged from eighteen months to seventy-plus years; males and females were about evenly divided in our group.

DOSAGE

The preparation used throughout this survey was a 5 mg scored tablet. The usual initial dose was one-half to one tablet daily and later modified in some instances from one-half tablet three times a day to one tablet twice a day. A few patients were placed on one tablet three times a day in order to study the maximum effectiveness and side reactions.

OBSERVATIONS

Patients were examined objectively, at weekly intervals as to their symptoms and clinical findings. Blood counts were taken at the begin-

TABLE I. RESULTS OF THERAPY

	Excellent	%	Good	%	Fair	%	Poor	%	Total
Children	14	10	38	26	13	9	8	5	73
Adults	8	5	46	30	14	9	9	6	77
Total	22	15	84	56	27	18	17	11	150 (100%)

ning of the survey, during the height of the pollinating season and at the termination of the ragweed pollinating season. Patients were questioned regularly as to their impression of the effectiveness of the drug and any untoward effects were noted and the dosage adjusted to suit the individual needs.

The 1953 ragweed pollen season was average for the Chicago area. However, the mold counts were the highest observed in this area for the past fifteen years.

CLINICAL IMPRESSIONS

1. Patients:

The drug seemed to become effective in fifteen to twenty minutes in most patients, and the benefits lasted for six to eight hours, although rarely yielding complete freedom from symptoms. Those individuals who had previously used other antihistamines, felt that FC-1 compared favorably with those previously used.

The patients reported the following types of side-reactions:

(a) drowsiness
(b) dizziness
(c) nervousness
(d) dryness of the mouth
(e) visual disturbances, with blurring or dilatation of the pupils
(f) hyperexcitability
(g) drug rash

2. Our own impression was that most patients experienced moderate benefits from FC-1. None of the side effects were of sufficient degree to require discontinuance of the drug, except for the few patients with visual disturbances and excessive dryness of the mouth. The largest number of side reactions was that of varying degrees of drowsiness, which could be controlled by adjusting the dosage without impairing the effectiveness of the drug. No cumulative action was noted. Of those patients who had complete differential smear studies, no evidence of alteration of the cellular elements was observed. Most changes seen in the blood picture were those that fit into the usual percentage error in laboratory technique.

PATIENTS WITH HAY FEVER AND OTHER ALLERGIC MANIFESTATIONS

1. Asthma was not controlled in any instance by FC-1. Such patients required other medication for control of symptoms.

2. Eczema: This drug proved about as effective as most in controlling pruritus.

3. Perennial Allergic Rhinitis: It was as effective as other antihistaminic preparations.

During the period that this survey was being made, a variety of allergic patients were seen in our offices. FC-1 was used in cases of urticaria and angioneurotic edema and was found to be fairly effective in the control of pruritus and the edema.

We also tried the drug in serum-sickness-like disease, especially those due to penicillin, resulting in some control of pruritus and edema, but no control of the disease entity.

This preparation was also used in several patients with contact eczematous dermatitis. Here, as above, only the pruritus was relieved.

Allergic patients with headaches were also given FC-1, with inconclusive results. The same was true of allergic patients with gastro-intestinal symptoms.

Identical doses of FC-1 were given to all age groups, with fewer side effects noted in the children.

Generally patients who had previously complained of side reactions to other antihistamines also complained of the same effects with FC-1, with the exception of those who complained of excessive dryness of the mouth or visual disturbances, which other antagonists did not produce.

SUMMARY

In summarizing our results, we can state that FC-1 has definite antihistaminic properties as well as the side reactions usually noted with other antihistaminic agents. Ragweed pollen patients reported that the drug was effective in about fifteen to thirty minutes and this effectiveness lasted from six to twelve hours. Of all patients subjected to observation, approximately 70 per cent reported good to excellent results, while 30 per cent reported fair to poor results. Children seemed to tolerate the drug better per pound of body weight than adults. Side reactions were noted in 18 per cent of the patients with relatively few serious ones. Several patients had to be discontinued on this drug because of excessive dryness of the mouth, and blurring of vision. This would indicate some atropine-like action. The optimum dose was 5 mg twice a day which could be tolerated by children and adults alike. In comparison to other antihistaminic agents, FC-1 exerted similar effects on allergies affecting the skin, respiratory, and gastro-intestinal tracts. No alteration in blood counts were noted at all. The data in the experimental animals would suggest that this drug should have had prolonged antihistaminic properties and lower toxicity in humans, which was not completely borne out.

CONCLUSIONS

1. A new antihistaminic compound with a chemical formula unrelated to other histamine antagonists is herewith reported.

2. In a series of 160 ragweed sensitive patients, 70 per cent reported good to excellent results with a 5 mg tablet administered twice a day.

3. Effectiveness was noted in fifteen to thirty minutes and lasted from six to twelve hours.

4. Side effects included those usually ascribed to other antihistamines such as mild drowsiness in about 15 per cent of the patients. In addition 5 per cent complained of dryness of the mouth and 3 per cent had blurring of vision with dilation of the pupils, which is not surprising since the compound has quite a similarity to atropine.

5. In other allergic syndromes, the effect was comparable to other available antihistamines.

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FIVE CONCEPTS PART OF EVERYDAY LIVING

University of Arkansas graduates in medicine, in pharmacy and in medical technology this year were urged to conduct an "honest and severe self-appraisal of personal qualifications—liabilities as well as assets."

Dr. Jacques P. Gray, director of special medical services for Parke, Davis & Company, Detroit, speaking at commencement exercises in Little Rock, also asked the graduates to "embrace five concepts as part of your being and everyday living."

He listed the five concepts as follows: Never flaunt your professional status; continue your quest for knowledge; be proud of your profession, but embrace the modesty and humility of the scientist; improve communications; and hold fast to your ideals and principles.

"The reward comes," Dr. Gray emphasized, "in gaining the status and stature of a very important person, not only as a member of the Health Service Team, but also as a mighty important citizen in your community.

"Then you will be the recipient from those whom you serve of their Respect, Reliance, and Responsiveness—all of which are among life's greatest and most satisfying values due you for a job well-done."

PRANTAL, ORALLY, IN THE TREATMENT OF ASTHMA AND NASAL ALLERGIES

A Preliminary Report

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VARIOUS drugs have been introduced from time to time for the treatment of pulmonary asthma and nasal allergies. None of these, including cortisone, has cured these conditions. Many, however, through different modes of attack, have produced high degrees of symptomatic relief. The untiring efforts of physicians have been directed towards experimenting with every new drug in an effort to raise the degree of symptomatic relief, prolong its duration and reduce toxic effects or side reactions to a minimum. In the instance of some drugs, like ethylene disulphonate, the theory supporting their use has seemed scientifically unsound, whereas in others, like histaminase, sound theory has been based on tenuous premises. Or in some, like Piromen, theory has been based on analogy and use on a therapeutic hope. However, sound theory is not necessarily the criterion of the results obtained from drugs.

Cognizance of the importance of bronchial secretions and bronchospasm in the development of asthmatic dyspnea quite naturally focused attention on the pathologic physiology responsible for these factors. The nerve supply to the bronchial tree received early investigation. Reinhoff and Gay[6] resected the posterior pulmonary plexus in an effort to alter the neurogenic effect on bronchial musculature and bronchial secretions. Selman[8] suggested that denervation of the vagal fibres is the best surgical approach to accomplish this. These procedures have had their disadvantages. It is natural to seek another approach. The possibility of accomplishing a "medical vagotomy" through the use of recently developed anticholinergic drugs capable of adequately blocking parasympathetic nerve impulses, presented itself as just such a hopeful new avenue of approach to this problem.

The clearly demonstrable anticholinergic effects of these drugs in the therapy of peptic ulcer[2,3] reduced the problem to the search for a drug with a minimum of side effects. Prantal (N,N dimethyl-4-piperidyline 1,1-diphenylmethane methylsulphate) is a quaternary ammonium derivative. It is soluable in water, methanol, ethanol and chloroform. Margolin et al,[4,5] have shown that Prantal administered orally prevented broncho-

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Prantal was supplied in 100 mg tablets along with placebo tablets through the courtesy of the Division of Clinical Research, of the Schering Corp.

Dr. Frank is from the Allergy Clinic, Los Angeles County General Hospital, Department of Medicine, University of Southern California.

Read by title at the Decennial Congress of the American College of Allergists, Miami Beach, Florida, April 9, 1954.

spasm and death of guinea pigs that would be caused by intravenous injection of acetylcholine. Studies in animals have shown a high safety ratio between toxicity and parasympatholytic dosages, and a lack of cumulative toxicity. Clinically,[2] administration of Prantal for months has not produced any acute or cumulative toxic effects in man.

The theory behind the use of anticholinergic drugs seems sound. We felt, if it were useful in asthmatics, it should have equal usefulness in nasal allergies where parasympathetic stimulation induces nasal mucosal secretions.

METHOD

We studied forty patients with Prantal, orally. An evaluation was made of the recent and current symptoms in each case, and the response to other medications. Then each patient was given a chart for the quantitative recording of daily symptoms and any and all medications taken. A new chart was used each week. Patients were very co-operative in the completion of their charts. Five of forty patients were given placebo tablets, exactly resembling Prantal, for several weeks prior to the use of Prantal. Besides this control group, comparative studies were made on seventeen patients with nasal allergies, who had previously taken antihistaminics. In the beginning, patients were started on 50 mg of Prantal four times daily, orally. Since this did not help asthmatics, all patients were subsequently placed on 100 mg four times daily—a dose quite tolerable and with negligible side effects. A few patients were tried on 200 mg four times daily with no increased benefits.

There were seventeen cases of asthma of which two had emphysema, five had hay fever and four had vasomotor rhinitis also. There were nine other cases of hay fever, one with eczema, and eleven cases of vasomotor rhinitis. We also included one case of angioneurotic edema and two cases of neurodermatitis. While on Prantal all other drug therapy was routinely discontinued, being allowed for emergency relief of symptoms only, and note thereof being made. In the neurodermatitis cases, local application of boric acid ointment was allowed as needed. All patients who were on desensitization therapy, continued such therapy. Prantal was used orally for not less than two weeks, and averaged about one month in patients who obtained benefit from it.

RESULTS

We have made no attempt to classify our asthmatics according to their severity of symptoms. At the time of the start of this study, all asthmatics were taking one or several drugs, usually several times daily for relief of symptoms. Some of our cases of allergic rhinitis had never had any other therapy, except antihistaminics, which the majority had tried.

Unhappily, despite sound theory behind its use, we found Prantal almost uniformly disappointing in its symptomatic relief of asthma. This

TABLE I. SYMPTOMATIC RELIEF OBTAINED BY ORAL USE OF PRANTAL RESULTS

Chief Symptom	Excellent 80-100%		Good 50-80%		Poor 0-50%		None No Help	
	No. of Cases	Percent	No. of Cases	Percent	No. of Cases	Percent	No. of Cases	Percent
Rhinorrhea	7	35	8	40	1	5	4	20
Sneezing	4	30.7	4	30.7	3	23.1	2	15.4
Post Nasal Drip	1	16.7	2	33.3	0	0	3	50
Chronic Nasal Blocking	1	12.5	0	0	0	0	7	87.5
Sinus Headaches	0	0	0	0	0	0	2	100
Chronic Sore Throat	0	0	0	0	0	0	1	100
Wheezing and/or Dyspnea	1	6.7	3	20	3	20	8	53.3
Coughing	0	0	0	0	0	0	2	100
Itching	1	25	0	0	1	25	2	50
Eczematoid Dermatitis	0	0	0	0	0	0	2	100
Edema of Lips	1	100	0	0	0	0	0	0
Total for All Respiratory Symptoms	14	20.9	17	25.3	7	10.4	29	43.3

TABLE II. RELIEF OF ALLERGIC DISEASE ENTITIES BY ORAL USE OF PRANTAL RESULTS

Allergic Disease Entity	Excellent 80-100%		Good 50-80%		Poor 0-50%		None No Help	
	No. of Cases	Percent	No. of Cases	Percent	No. of Cases	Percent	No. of Cases	Percent
Asthma	0	0	2	33.3	2	33.3	2	33.3
Asthma with Emphysema	0	0	0	0	0	0	2	100
Asthma* with Hay Fever	0	0	0	0	1	20	4	80
Asthma* with Vasomotor Rhinitis	1	25	1	25	0	0	2	50
Total Asthmatics	1	5.9	3	17.6	3	17.6	10	58.8
Hay Fever	2	25	3	37.5	1	12.5	2	25
Hay Fever* with Asthma	2	40	0	0	0	0	3	60
Hay Fever with Eczema	0	0	0	0	1	100	0	0
Total Hay Fever	4	28.6	3	21.5	2	14.3	5	35.7
Vasomotor Rhinitis	2	18.2	3	27.3	1	9.1	5	45.4
Vasomotor Rhinitis* with Asthma	1	25	1	25	1	25	1	25
Total Vasomotor Rhinitis	3	20	4	26.6	2	13.3	6	40
Total Nasal Allergies	7	24.1	7	24.1	4	13.8	11	37.9
Total Respiratory Cases	5	13.5	9	24.3	6	16.2	17	45.9

*Relief of first disease mentioned considered only.

does not correspond with Seidmon and Schaffer's results to be discussed later, but does with those of Dann et al[1] when they used Prantal. By virtue of its same anticholinergic properties, Prantal, orally, proved reasonably helpful in the treatment of nasal allergies.

As may be seen in Table I, results were best with rhinorrhea, somewhat less so with sneezing and quite disappointing with chronic nasal blocking. To sum these up, briefly, symptomatically we obtained good or excellent results in 75 per cent of cases with rhinorrhea, 61.4 per cent in cases of sneezing and only 12.5 per cent in cases of nasal blocking. Wheezing and dyspnea responded well in 26.7 per cent of the cases. Table II illustrates that the results appear slightly differently when each case is considered as a disease entity consisting of several symptoms. Twenty-three and one-half per cent of all asthmatics obtained good to excellent results, 50.1 per cent of all hay fever cases were similarly helped, while 46.6 per cent of

cases of the vasomotor rhinitis were so helped. Forty-eight and two tenths per cent of all cases of nasal allergy were helped. The one case of angioneurotic edema obtained 100 per cent relief but relapsed with discontinuance of therapy. The two cases of neurodermatitis were not helped at all. Summed up and grouped as a whole, good to excellent results were obtained in 37.8 per cent of all cases of asthma and nasal allergies. In one of the five cases treated with placebo pills a result as good as with Prantal was obtained. Of twenty-nine cases with nasal symptoms, twelve had never been put on antihistaminic therapy. Of the remaining seventeen who had tried one or another antihistaminic, nine or 53 per cent felt better on antihistaminics than Prantal, five or 29.4 per cent felt worse on antihistaminics than on Prantal and three or 17.7 per cent felt the same, in this instance, poorly on both types of medication.

DISCUSSION

Seidmon and Schaffer,[7] thinking along the lines of a "medical vagotomy" tried the use of Prantal, by mouth. They reported on the treatment of fifty cases of asthma with Prantal in doses of 50 mg four times daily and twenty-six cases of asthma with Prantal in combination with Chlor-trimeton 4 mg four times daily. They obtained slightly better results in the cases treated with Prantal alone, and averaged 75 per cent with moderate to excellent relief—a good accomplishment for many a drug. Vickers[9] had tried the use of Prantal in doses of 10 to 15 mg intramuscularly, in acute asthmatic episodes with relief in two to five minutes. It was of no special benefit in status asthmaticus. Recently, Dann, Brown and Kupperman[1] reported on the use of Prantal, intramuscularly, in the treatment of asthma. By means of spirometric studies they showed the results in varying stages of asthma obtained from an intramuscular injection of 25 mg of Prantal were better than those obtained from an injection of 50 mg of Ephedrine, 0.5 gm of aminophyllin or 0.25 mg of epinephrine. They also tried Prantal, orally, in nine asthmatics without significant demonstrable improvement, clinically, or in vital capacity or maximal breathing capacity. From this they concluded the drug, by mouth, was either poorly absorbed or inactivated. Analyzing the results of Vickers and Dann et al and our own, we believe this may be the factor accounting for their good results by the intramuscular route and our relatively poor ones in asthmatics by the oral route. We were unable to duplicate Seidmon and Schaffer's results in asthmatics. Our reasonably good results in nasal allergies treated by the oral route suggests that perhaps not as great a concentration of the drug is essential to affect the parasympathetic nerve or the ganglion regulating the nasal mucosa. Dann et al did not mention how long their patients were benefited. Clinically, most patients who did not take Prantal regularly soon relapsed. However, a few nasal cases seemed to have had prolonged benefits after discontinuance of therapy. We are inclined to judge this as a non-specific effect.

From a patient convenience and economy viewpoint, an oral preparation would appear most desirable, provided a suitable therapeutic blood level could be obtained with a minimum of side effects. At 100 mg four times daily, distressing dryness was negligible. One patient had temporary diplopia. Prantal appears to have a place in the array of drugs with a good degree of usefulness in the symptomatic relief of nasal allergies. This we believe because it produces even by oral administration over a 50 per cent degree of relief in two major symptoms and with a minimum of side effects. We have had no experience with the effect of Prantal on rhinorrhea and sneezing in the East during the ragweed season. It is quite conceivable that Prantal, orally, might prove ineffective in this environment.

CONCLUSIONS

Prantal methylsulphate, a new anticholinergic drug, was administered, orally, to seventeen asthmatics, nine with a nasal allergy, and to twenty other cases of nasal allergy, with a minimum of side reactions. The drug, orally, did not satisfactorily relieve asthmatic symptoms but showed a relatively high degree of symptomatic relief from sneezing (61.4 per cent) and rhinorrhea (75 per cent). Prantal, we feel, is worthy of further investigation.

REFERENCES

1. Dann, S.; Brown, F. R., and Kupperman, H. S.: The use of Prantal in asthma: A spirometric evaluation. J. Allergy, 24:532, 1953.
2. Heineken, T. S.: A new cholinergic blocking agent in the treatment of duodenal and gastric ulcers. Am. Practitioner, 3:701, 1952.
3. Kirsner, J. B.; Palmer, W. L.: Levin, E., and Klotz, A. P.: Gastric antacid and anti-secretory drugs. Ann. Int. Med., 35:785, 1951.
4. Margolin, S.; Doyle, M.; Giblin, J.; Makovsky, M.; Spoerlein, T.; Stephens, I.; Berchtold, H.; Belloff, G., and Tislow, R.: Pharmacological properties of a new parasympathetic blocking agent, N,N-dimethyl-4-piperidylidene 1,1 diphenylmethane methylsulphate (Prantal). Proc. Soc. Exper. Biol. & Med., 78:776, 1951.
5. Margolin, S.; Makovsky, A.; Spoerlein, M. T.; Stephens, I., and Tislow, R.: A new selectively acting parasympathetic blocking agent: N,N-dimethyl-4-piperidylidene 1,1 diphenylmethane methylsulphate (Prantal). J. Pharmacol. & Exper. Therap., 103, (Dec.) 1951.
6. Reinhoff, W. F., and Gay, L. N.: Treatment of bronchial asthma by bilateral resection of posterior pulmonary plexus. Arch. Surg., 37:456 (Sept.) 1938.
7. Seidmon, E. E. P., and Schaffer, N.: Prantal methylsulphate, a new parasympathetic blocking agent, in the treatment of bronchial asthma. Ann. Allergy, 11:43, (Jan.) 1953.
8. Selman, M. W.: Denervation of the lungs for bronchial asthma; case report. Ann. Allergy, 8:328 (May) 1950.
9. Vickers, M. A.: Clinical trial of Prantal methylsulphate in acute asthmatic attacks: Preliminary report. J. Maine M. A., 43:381, (Dec.) 1952.

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Case Report

HYPERSENSITIVENESS TO HUMAN PITUITARY

Case Report

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The subject of this report is a twenty-five-year-old white man who was first seen on December 15, 1950. He had a severe head injury at the age of six years. Symptoms of excessive urinary output and thirst were progressive during the next three months, and sometime during the following year the diagnosis of diabetes insipidus was made. Various pituitary preparations were tried for the relief of symptoms. The inhalation of posterior pituitary powder was found to be the most satisfactory. It was first used in 1937.

In 1944 the patient experienced his first attack of asthma which he associated with a "cold." This attack occurred two weeks after an illness which was diagnosed as bronchial pneumonia. It was the only wheezing attack which occurred that winter. While at college the following winter, he had numerous attacks of coughing and wheezing which he usually associated with "colds."

In 1946 radium was applied to the nasal mucous membrane by an otolaryngologist to control "sinus trouble." There was improvement until the next winter when attacks of asthma again occurred.

In 1947, he first began to associate some asthmatic attacks with the inhalation of the pituitary powder which, at this time, he had been using daily for ten years. At first he noticed a delay of four to eight hours before asthma appeared but later this time interval was shortened. On one occasion he refrained from using the pituitary extract for a week and during that time he experienced no attacks of asthma. After definitely establishing the relationship between the attacks of asthma and the inhalation of pituitary powder, he reduced the use of the extract to a minimum, rarely more often than two or three times weekly.

At the time of his initial visit to the office, the patient could readily demonstrate an attack of asthma at will. The attack would usually occur within a few seconds after the inhalation of the pituitary powder. The symptoms were rather severe and would last from thirty minutes to three or four hours, and not infrequently there would be come discomfort on the following day. About two years ago he was able to prevent an attack of asthma by premedication with an antihistamine and a small dose of ephedrine taken twenty to thirty minutes before inhaling the powder. However, this procedure eventually became less and less effective in preventing symptoms. Finally, the wheeezing became so distressing following the inhalation of the posterior pituitary powder, that the patient would not use it unless he anticipated being in a situation where it would be inconvenient or embarrassing to have to void every fifteen or twenty minutes.

This individual also has experienced perennial nasal symptoms of an allergic nature for several years which are most marked during the winter months. He knew that house dust caused sneezing and watering of the nose, and sometimes nasal

From the Allergy Clinic, Kansas University Medical Center, Kansas City, Kansas. Presented at the Decennial Congress of the American College of Allergists, at Miami Beach, Florida, April 8, 1954.

stuffiness, but not coughing or wheezing. According to the history, his father has had "sinus trouble" for as long as the patient can remember, and his younger brother has asthma.

The physical examination was essentially normal, except that the nasal mucous membrane was pale and swollen and there was partial obstruction of the air passages of the nose. Routine laboratory studies were within normal limits.

A solution of posterior pituitary extract was prepared by defatting 1 gram of commercial posterior pituitary powder (the same that the patient had been inhaling) with ether, and then extracting with 50 cc of equal parts of Coca's fluid and glycerine. The mixture was placed in the refrigerator to extract for forty-eight hours and then was filtered and sterilized with a Seitz filter. This crude pituitary extract was used for skin testing and for treatment.

There were strongly positive scratch and intradermal cutaneous reactions to the posterior pituitary extract and definite, although less pronounced, skin reactions to house dust. The remainder of some eighty skin tests to various ingestants and inhalants were negative and were also of no significance clinically.

Specific treatment consisted of the hypodermic administration of gradually increasing amounts of the crude posterior pituitary extract until tolerance was reached (.05 cc of 1-50 dilution). This dose was administered at weekly intervals for a period of two years. The clinical sensitivity to pituitary preparations was definitely reduced during this time but there was little or no change in the degree of skin sensitivity. The patient has now been instructed in the self-administration of pitressin tannate in oil. He has found it necessary to administer two or three 1 cc ampules of this material weekly in order to remain comfortable. Occasionally a transient local swelling with erythema and itching at the site of an injection is noted but otherwise no undesirable side effects are reported. Furthermore, this individual claims that he not only has been free of asthma for over a year, but also that his urinary output is adequately controlled.

IMMUNOLOGICAL CONSIDERATIONS

Data were available in the literature on twenty-eight persons with sensitivity to pituitary extracts, two of whom had had diabetes insipidus. There have been few attempts to determine whether the sensitivity was organ or species specific and especially whether the sensitivity included human as well as other animal glands.[1-8]

Simon and Ryder[6,8] have studied hypersensitivity to pituitary in five patients (all of whom had been sensitized by injection of posterior pituitary extracts). They obtained positive direct skin tests to beef, pork, dog and human pituitary, thus indicating that the antigen is gland specific. Also, they suspected that the antigen was not one of the pharmacologically active principles of the pituitary gland. Passive transfer tests with *human pituitary*, however, were not definitely positive.[7]

Natt[3] resported that "with the co-operation of the manufacturer we were supplied with an extract in which the active substance has been destroyed. Both direct and positive transfer tests with this material were negative. This would seem to indicate definitely that the sensitivity was to the active principle of the posterior pituitary substance." The method of destroying the active principle was not described in Natt's paper, however. Parke, Davis Laboratories have recently reported that vasopressin is a highly stable substance and resists inactivation by a number of methods.[5] It is quite possible that any procedure which would inactivate the vasopressor substance would also alter other substances in the extract.

Feinberg, et al,[1] reported a case of allergy to pituitary corticotrophic hormone in which there were positive skin reactions to posterior as well as anterior pituitary preparations. These authors felt that the sensitivity was to a hormone, in this case to anterior pituitary corticotrophic hormone.

Skin tests on the patient in the present study confirm Simon's observation[6,8] that the antigen is gland specific and not species specific and also Feinberg's observation[1] that anterior and posterior pituitary preparations, as obtained commercially, have similar antigenic properties.

Table I.

DIRECT SKIN TESTS

	FULL STRENGTH	1:10 DILUTION	1:50
PITRESSIN 20u/cc. (PARKE, DAVIS)	+	+	—
PITUITRIN 5u/cc. (PARKE, DAVIS)	+	+	—
PITOCIN (PARKE, DAVIS)	+	+	—
ANT. PIT. LIQUID (ARMOUR)	+	+	—
ANT. PIT. LIQUID (SHARPE & DOHME)	+	+	—
ACTHAR GEL - PORK (ARMOUR) 1:5 IN SAL.	+	—	—
ACTHAR - BEEF (ARMOUR) 5u/cc.	IRRITATING TO NORMAL SKIN	+	+
GELATIN (ARMOUR) 1:5 IN SALINE	—	0	—
APL CHORIONIC GONADOTROPIN (AYERST, McKENNA, HARRISON)	IRRITATING TO NORMAL SKIN	0	—

Table I summarizes the results of direct intradermal skin tests to a number of commercially available pituitary substances. All of the pituitary preparations gave reproducible positive tests. The gelatin vehicle for Acthar Gel gave negative tests. APL chorionic gonadotropin, which is similar in action but not identical with pituitary gonadotropin, gave negative skin reactions when properly diluted.

It is worth noting that the crude extracts, whether derived from the anterior or posterior lobe, gave larger skin reactions than the more refined ones. The anterior pituitary liquid (Sharp and Dohme) had an amber color which more nearly resembled the appearance of the crude extract which was prepared as described above for the treatment of this patient and it produced the largest skin reaction of any of the commercial preparations.

This work is supplemented with the successful demonstration of the passive transfer test to human pituitary. Table II shows the results of direct intradermal skin tests, normal skin control on a test subject, and indirect passive transfer tests on the same test subject to beef, pork and human pituitary glands. The extracting fluid acts as a control and the human muscle, liver and brain were included to emphasize the gland specificity of the pituitary antigen.

The beef, pork and human pituitary extracts were made by separating the lobes of the fresh gland by blunt dissection and macerating each lobe in five volumes of Coca's fluid, without defatting. After extracting for twenty-four hours in the refrigerator the supernatant fluid was sterilized by passing through a Swinny filter and this material was used undiluted for scratch and intradermal tests. New glassware, syringes and needles were used throughout. In order to avoid possible antigenic contamination by the Swinny filter another human gland was obtained and the experiment with the human pituitary extract was repeated without filtration.

In each instance, when doing the passive transfer tests, it was observed that the injection of human pituitary extract into a non-sensitive site gave a negative reaction, that injection of extracting fluid into a sensitized site gave a negative reac-

tion, whereas, injection of human pituitary extract into a sensitized site gave a positive reaction.

The patient's serum was found to be negative for precipitins using the crude pituitary extract as the antigen and employing the agar-plate diffusion technique.

Table II.

	PATIENT	TEST SUBJECT (CONTROL)	TEST SUBJECT (SENSITIZED SITE
ANT. PIT. BEEF	+	0	+
POST. PIT. BEEF	+	BLANCHING	BLANCHING & +
ANT. PIT. PORK	0	—	—
POST. PIT. PORK	+	—	—
[1]ANT. PIT. HUMAN	+	0	+
[1]POST. PIT. HUMAN	+	BLANCHING	BLANCHING & +
[2]ANT. PIT. HUMAN	+	0	+
[2]POST. PIT. HUMAN	+	0	+
EXTRACTING FLUID	0	0	0
HUMAN MUSCLE	0	—	—
HUMAN LIVER	0	—	—
HUMAN BRAIN	0	—	—

1 = MAY, 1953 2 = JAN., 1954 ALLERGY CLINIC - K.U.M.C.

The patient's serum was also tested for complement-fixing antibodies and none were demonstrated. Both the serum and the antigen were shown not to be anti-complementary. Furthermore, a portion of serum was heated to 56° C for one hour. It was found that this treatment inactivated the skin sensitizing properties of the serum.

It should be pointed out that it is doubtful that any of the pituitary preparations are pure anterior or pure posterior lobe extracts. It is difficult to obtain an exact separation of the two lobes and methods of purification may remove physiologically significant amounts of a contaminating hormone or other substance, but do not necessarily remove immunologically reactive amounts. The patient developed sensitivity to a mixture of possible antigens while using the posterior pituitary powder and was skin tested with an extract of this powder as well as other similar mixtures. In view of this fact it would not be possible to make statements concerning the exact nature of the antigen. It has been observed that the antigen as well as the skin blanching properties of the posterior pituitary extracts resist boiling, pepsin digestion, boiling with N/10 hydrochloric acid, and digestion with takadiastase. Additional investigations are planned with the hope of learning more about the nature of the antigen.

SUMMARY

This patient is of the type generally regarded to be an atopic individual. He has a positive family history for allergy and he, himself, has multiple manifestations of allergy. Sensitization developed after prolonged exposure by inhalation of small quantities of posterior pituitary powder. This sensitization has been shown to be specific for an antigen found in human pituitary as well as other mammalian pituitary glands. A thermolabile, skin sensitizing antibody, specific for this antigen, was demonstrated in the patient's serum. Crude extracts produced larger skin reactions than refined ones. Precipitins and complement-fixing antibodies were not found in the patient's serum with the methods used. Clinical sensitivity to

inhalation and injection of pituitary extracts was greatly reduced, although not abolished, by specific antigen therapy. Skin sensitivity remained unchanged.

ACKNOWLEDGMENTS

Dr. Perry Morgan, Assistant Professor in the Department of Microbiology, University of Kansas Medical Center, Kansas City, Kansas, performed the tests for precipitins and complement-fixing antibodies.

Armour Laboratories supplied the Acthar Beef and the gelatin vehicle for Acthar Gel and Ayerst, McKenna, Harrison supplied the APL chorionic gonadotropin used in testing this patient. Parke, Davis Laboratories were very co-operative, although unsuccessful, in their attempts to prepare an inactivated posterior pituitary extract for skin testing.

BIBLIOGRAPHY

1. Feinberg, Samuel M., Feinberg, Alan R. and Bigg, Edward: Allergy to pituitary corticotrophic hormone. J.A.M.A., 147:40, 1951.
2. Harten, M., and Walzer, M.: Allergy to insulin, liver, pituitary, pancreas, estrogens, enzymes, and similar substances. J. Allergy, 12:72, 1940.
3. Natt, J.: Diabetes insipidus with sensitivity to posterior pituitary hormone: case report. Virginia Med. Month., 77:134, 1950.
4. Plass, John B.: Hypersensitivity to pitressin. J. Clin. Endocrinol., 9:650, 1949.
5. Sharp, E. A.: Personal communication, 1954.
6. Simon, Frank A.: Hypersensitiveness to pituitary extract. J.A.M.A., 104: 996, 1935.
7. Simon, Frank A.: Personal communication, 1953.
8. Simon, Frank A., and Ryder, C. F.: Hypersensitiveness to pituitary extracts. J.A.M.A., 106:512, 1936.

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Alevaire "Mist" (Winthrop-Stearns) is an aqueous solution of a new nontoxic detergent in combination with other mucolytic ingredients. It has been found effective in a wide number of respiratory conditions in infants, including neonatal asphyxia and diphtheria, as well as bronchial asthma in adults and children. Its function is dissolving viscid secretions in the air passages. No complicating results have been noted from its use.

Experience with the inoculation, now going on of one and one-half million children with the Salk vaccine for poliomyelitis, will be presented at the Eighty-second Annual Meeting of the American Public Health Association in the Memorial Auditorium in Buffalo, New York, October 11 to 15, 1954.

Progress in Allergy

MISCELLANEOUS REVIEW OF ALLERGY 1953

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The choice of material for this review must rest in those publications which hold interest for the average allergist. Though it may seem repetitious, an apology is again extended to those authors whose articles are well worthy of review but whose substance does not carry sufficient general interest to be included. As in the past, a division of the reviewed material will assist those readers who desire specific references rather than the miscellaneous grouping as a whole.

EDUCATION

According to Brown[15] allergy is one of the youngest subdivisions of medicine and has the shortest modern history. This is based entirely upon the lack of acceptance of three basic hypotheses. The first of these is that a particular group of human beings could be affected by everyday substances. The second concept, which was difficult to be accepted by the lay or medical human mind, was the actual observation that the first and sometimes many subsequent exposures to the above substances led to no overt signs or symptoms. The third concept, difficult to be accepted, was that the specific responses to known sensitizing agents could be induced by non-allergenic or physical agents as well as by emotional and mental states. In this history of allergy, Brown adequately reviews the basic work in this specialty as well as citing some interesting historical facts. For example, approximately 150 years ago a physician advised his asthmatic patients to abandon the practice of smoking, with great advantage to their health. Potassium iodide* was originally used for asthmatic patients in 1848. Epinephrine was first injected subcutaneously for the relief of bronchial asthma in 1903. Ephedrine came into general use in 1917. The author mentions the introduction of more recent preparations such as aminophyllin in 1935 and the antihistaminic preparations in 1939. Brown emphasizes that in spite of all so-called cures, none of them has supplanted the best treatment of allergic diseases—elimination and injection therapy. As Brown states in his closing paragraph, it will be interesting to read another history of allergy in 1973 to see what has transpired in the intervening twenty years.

**The Boston Medical and Surgical Journal* an original communication on "Nitrate of Potassa in Asthma" by H. T. E., November 29, 1848, published in ANNALS OF ALLERGY, Vol. 12, No. 2, March-April, 1954.

Thomas[142] decries the lack of proper emphasis on the importance of allergic diseases at the undergraduate level. Young men should be trained at the resident level after having a broad base of experience in fundamental sciences and clinical medicine. According to the writer there are just thirteen institutions in the United States approved by the Council on Medical Education of the American Medical Association for the proper training of residents in allergic diseases. Only these thirteen institutions possess qualifications for teaching the diagnosis and treatment of allergic diseases. It is little wonder that there is great difficulty in attracting high grade men in medicine to undertake the specialty of allergy. It is the moral obligation of every well-trained allergist to see that the men who "dabble in allergy" are given a more adequate understanding of this subject. Thomas believes that the Foundations pertaining to allergy do indicate a step forward in allergy education and research at the undergraduate and postgraduate levels.

Spain[129] states that the clinical sensitiveness of an individual represents an intensive effort of the individual against the invading antigen. This is true whether or not it is considered that the sensitivity of the individual results from inheritance, overwhelming contact, or exposure to an antigen with high sensitizing properties. He divides the clinical forms of allergy into the skin sensitive and the skin negative types. In the former group he subclassifies this into hereditary and non-hereditary allergic disease. In the latter section the subdivisions are non-infective and infective. The skin sensitizing antibody may occur spontaneously or it may have been induced. This skin sensitizing antibody, which is essentially a human antibody, was so named because its presence can be demonstrated readily only by the direct or indirect skin test. This skin sensitizing antibody should not be confused with another antibody appearing in the serum of hay fever patients who have been adequately treated with specific pollen extracts. This latter antibody, discovered by Cooke, has been termed the blocking antibody. In this well prepared paper Spain discusses the immunology of allergic disease.

It is recognized that one of the most important steps in the adequate management of an allergic patient is the removal of the substances causing the patient's distress. If this is impossible, specific therapy with allergenic extracts is always advised. However, at times it may be necessary for the patient to remove himself from the cause by means of migration. Overenthusiastic and thoughtless application to this principle of migration, however, often does great harm. An editorial[35] states that the careful analysis of the case records of those who are apparently cured by migration, obtain their true improvement by the concurrent application of some recognized measure, such as the removal of household pets. Before any move is made for the relief of allergic symptoms, it is considered essential to determine whether the new climate will indeed effect an improvement. It is also necessary to determine whether or not the patient can live in the

new community without being a ward of a local charity. A greater effort should be made to identify the causative allergens and to find a suitable treatment that can be applied without a change of residence. Individualization of treatment has been an important feature in the proper care of any allergic patient. It is just as important for the physician to recognize which of his patients will benefit from a change of climate and which will continue to have their symptoms in their new locality.

The creation of a harmonious team between a general practitioner, patient and allergist is suggested by Criep.[28] In this co-operative effort it is necessary that the family physician familiarize himself with all instructions given to his patient. The consulting allergist, at the same time, should acquaint the referring physician with specific and non-specific measures employed in the treatment of the allergic condition. This reviewer recommends this excellent article for the allergist in practice.

Abramson[1] uses the term psychosomatic to indicate a mind-body integrated function rather than purely psychogenic. In the first part of his special article he has reviewed various papers pertaining to psychosomatic allergy that have been published in recent years. In the second part of his presentation he has illustrated schematically the many factors which inevitably enter into adequate therapy. His verbatim recorded interviews would indicate that the management of patients with various syndromes of allergy requires consideration of the parental-child association and the influence of the physician upon this family constellation. It is the feeling of this author that the function of the specialist in allergy is to manage the patient as a whole and to integrate the mind-body functions of his patients.

TISSUE REACTIONS

A phenomenon of altered tissue reactivity, the Shwartzman phenomenon, has been reviewed by Rostenberg[119] with consideration for its widespread clinical ramifications. In the preparation of the experimental animal (usually a rabbit) bacterial products are injected into the skin, a vascular system of an organ, or into the general circulation of the animal. After an incubation period of twelve to twenty-four hours, the provocative injection of bacterial products or antigen to which the animal is sensitive is given by intravenous administration. It must be stressed that whatever route is used for the preparatory injection, the eliciting material must be given intravenously. Following such procedures, hemorrhagic necrotic reactions appear at the skin site. Such microscopic hemorrhage is followed by necrosis. Many allergists confuse the Shwartzman phenomenon with the Arthus reaction. It might be well in this review to bring out some of the differentiating features between these two important and interesting types of reaction.

In the subject showing the Shwartzman type of phenomenon the single injection will prepare the host for the subsequent necrosis appearing after the intravenous administration of either bacterial products or antigens to

which he is sensitive. In the Arthus phenomenon the preparation is determined by one or more injections, and the elicitation is determined by the administration of the material into the tissue that will eventually show the necrosis. The Shwartzman phenomenon can be elicited by microorganisms or their products, whereas the Arthus phenomenon must be elicited by the administration of proteins or complex polysaccharides. A wide variety of eliciting substances will produce the Schwartzman phenomenon, whereas the Arthus phenomenon must be produced by the same material as that used for the preparation of the host. Microscopic hemorrhage is followed by necrosis in a period of four hours in the Shwartzman phenomenon and the same length of time in the Arthus. The preparation—incubation period in the Arthus phenomenon is nine days, whereas in the Shwartzman type the preparation is only twenty-four hours. There is no degree of specificity in the Shwartzman type, but a high degree of specificity has been determined in the Arthus. The latter type of reaction requires precipitating antibodies, whereas there are none in the Shwartzman type. The pathology of the Arthus phenomenon consists of capillary thrombosis and rupture with subsequent hemorrhage into the tissue followed by necrosis. In the Shwartzman phenomenon the pathology is primarily that of capillary thrombosis and rupture with subsequent hemorrhage into the tissues and necrosis. It is seen, therefore, that these two are essentially different although there are marked points of similarity in their mechanisms. Rostenberg feels that the true definition of allergy—"an acquired specific alteration in the capacity to react brought about by an antibody mechanism"—excludes the Shwartzman phenomenon, which probably represents the summation of the effects of two irritants. Clinically it is felt that the following conditions may possibly develop as a result of the Shwartzman mechanism: bilateral renal corticle necrosis, Waterhouse-Friderichsen syndrome and ulcerative colitis. Cutaneous conditions include purpura, pyoderma gangrenosa, dermatitis gangrenosa infantum, dermatitis nodularis necroticia and Lazarine leprosy. Many of the bizarre manifestations that are now labeled as hetroallergic manifestations may be of the nature of the Shwartzman phenomenon.

Thomas and Good[140] have reported on their studies with the generalized Shwartzman reaction. This generalized type reaction could not be elicited in animals prepared by meningococcal toxin administration, by non-bacterial materials such as starch, kaolin, rabbit liver, glycogen or human serum. It was in this respect that the general Shwartzman phenomenon differed from the local type described above by Rostenberg. The animals used by Thomas and Good showed no gross pathological changes if death occurred within four hours of the second injection. Those animals which died after four hours, or which were sacrificed at the end of twenty-four hours, showed bilateral cortical necrosis of the kidneys. The severity of the lesions was dependent entirely upon the doses of toxin administered. Hemorrhagic areas were quite widespread, being dependent upon the

extensiveness and severity of the renal lesions. In the kidneys, eosinophilic plugs were found, but their presence could not be observed in any other organ. Renal necrosis could not be produced in these laboratory animals if the intervals between injections were less than six hours or over ninety-six hours. The mortality rate in the laboratory animals was increased by the administration of cortisone. Nitrogen mustard administration by intravenous route inhibited the Shwartzman phenomenon. Protection of the bone marrow by clamping the aorta for five minutes after the injection of nitrogen mustard did not inhibit the Shwartzman phenomenon. In this latter instance, leukopenia did not occur; but in the former instance the circulating polymorphonuclear leukocytes did show a marked drop in thirty minutes after the initial injection of toxin. Thomas and Good[141] also have reported rather extensively on the administration of large dosages of cortisone from two to four hours prior to the intravenous injection of toxin to rabbits. It was found that this procedure did inhibit the development of the Shwartzman reaction. When cortisone was given in a dosage of 25 mg daily for four days, inhibition of the reaction did not occur. The renal lesions produced by toxin administered after cortisone were widespread and characterized by parenchymal hemorrhage. There was necrosis of the glomeruli and tubules within the cortex. The medulla was rarely involved. The protective effect of nitrogen mustard was associated with polymorphonuclear leukopenia resulting from the mustard administration. The protective mechanism of nitrogen mustard did not depend upon kidney exposures as indicated by the lack of affection upon the results when one kidney was clamped. The authors feel that there is a close similarity between skin and kidney lesions produced by a single injection of toxin in cortisone treated rabbits and the lesions of local and generalized Shwartzman phenomenon. They postulate that cortisone treatment may reduce the capacity of lymphoid tissue and other cells to remove or retain toxin from the circulating blood.

It has been noted above that the Arthus phenomenon is prepared by the administration of protein material in one or more injections. Elicitation of this phenomenon is determined by the administration of the same material as that used for the preparation of the reacting site. Croxatto[32] administered intradermal injections of histamine to rabbits and guinea pigs. The dosage varied from two to forty-seven times the calculated minimal intravenous dose for an animal of comparable weight. After a single injection typical lesions seen in the Arthus reaction failed to appear. It was the author's conclusion that histamine was not the cause of the Arthus phenomenon inasmuch as the single massive intracutaneous injection of this material did not produce the typical reaction.

CAPACITY FOR SENSITIZATION

Wittich[154] in addressing the European Congress in Denmark called to the attention of the Congress that no tissue could escape allergic manifesta-

tions. He emphasized that every cell in the body shares in allergic disease although this might be apparent only as a major cause of difficulty in the chief shock organ affected. He stated that the allergist is forced to deal with many types of phenomenon. Few allergens demonstrate a single action as in pollen, vaccine and drugs. Few patients respond with only one type of reaction. His remarks were concluded with the thought that allergy is unique since it applies to all of the other medical specialties. It requires the combined efforts of physicians and scientists for the purpose of promoting and advancing the study, laboratory and clinical knowledge of allergy.

That the capacity to become sensitized is almost universal is the statement of Harkavy and Perlman.[54] Though this sensitivity may vary in degree, the presence of allergy in an individual is dependent upon heredity, conditions which make the tissue receptive to such stimulation, the nature of the allergenic excitant and the intensity of the exposure. Their remarks concerning the influence and presence of allergy as regards prolonged illness have been divided into the various sections of the allergic field. The majority of their presentation is devoted to a consideration of the pathogenesis and clinical course of the more common allergic conditions as eczema, bronchial asthma and its sequelae.

CARDIOVASCULAR SYSTEM

The cardiovascular system may also be a shock organ for an allergic reaction. Kern[64] feels that the growing frequency of exposure and sensitization of patients to allergens is the reason why allergy is growing in importance in relation to the cardiovascular system. The usual edema and smooth muscle spasm which occur in bronchial asthma are completely reversible. The symptoms of seasonal hay fever, with a swollen mucosa, are entirely returned to normal within a few hours after the end of the pollen season. Kern emphasizes, however, the more severe and prolonged allergic reactions which result in organic destructive, irreversible changes. The recognition of such procedures is evidenced by the increase in instances of periarteritis nodosa, which in itself is an expression of an irreversible allergic tissue reaction. Many authors have commented upon the frequent association of periarteritis nodosa with bronchial asthma. This has been sufficiently remarkable to consider the development of periarteritis nodosa in all asthmatics whose eosinophile percentage rises above 25 per cent. This is particularly true if the patient complains of pain in his extremities. Kern emphasizes that there must be distinction made between those conditions in which the cardiovascular system is the shock organ and those in which the cardiovascular phenomenon may be affected through nervous stimuli from other sources elsewhere in the body. He considers the distinction to be made between these mentioned and those in which the mechanism produces the effect upon the cardiovascular system through an etiologic agent of unknown origin and action. The heart muscle itself can

be involved as a part of periarteritis nodosa. The involvement of the heart as a shock organ in this disease can be proven. Paroxysmal auricular tachycardia, extrasystoles and paroxysmal auricular fibrillation may all be a part of the usual benign pattern of most allergic diseases. However, this does not necessarily indicate that the cardiovascular system itself is the shock organ, but that the influence resulting in the above cardiac arrhythmias may be a part of an allergic reaction elsewhere in the body. In patients with bronchial asthma, fibrosis and emphysema are of the most serious importance to the circulatory system. These pulmonary complications definitely influence the life expectancy of most asthmatic patients. He is in hopes that the discovery of the basic mechanism of the allergic reaction will reveal new ways in which allergy affects the heart and blood vessels so that more rational and effective treatment may be instituted at an earlier time.

TOBACCO EFFECTS

Recent publicity has brought to light the marked importance of cigarette smoke as a likely cause of bronchogenic carcinoma. Friedell[44] has written of the effect of cigarette smoke on the peripheral vascular system. The inhalation of tobacco smoke, according to this author, will produce vasoconstriction because of its nicotine content. He employed the use of albumen tagged with I^{131} This material was given intravenously according to the method of Kreger.[69] With alterations in blood volume, radioactivity will be increased or decreased. These changes in radioactivity will reflect the change in blood volume in a cross-section of the area measured rather than of the surface only. The per cent change of radioactivity would indicate an equivalent change in blood content of the volume measured. One hundred persons with presumably normal circulation were tested by the means described above. Friedel found that seventy-nine of the persons tested were sensitive to ordinary cigarette smoke. With a new type of filter, cigarette smoke did not cause any reaction in one out of three persons tested. This finding would indicate that the nicotine and other alterative factors were removed in a certain percentage to a level at which the patient did not receive enough vasoalterative substance to produce changes in the radioactivity of the part measured. The fingertips were used for the measurement of this change. The maximum response of radioactivity change occurred in eight to ten minutes after the person began to smoke. Men seemed to recover more quickly after smoking than did women. From his work, Friedel has indicated that the principle of filtration of tobacco smoke is probably a good one; and he indicates that women need this more than men.

In opposition to this report is the work done by the chemical laboratory of the American Medical Association.[21] These reporters employed an automatic smoking machine in which about two-thirds of each cigarette was smoked using thirty-five ml puffs of two seconds duration taken once a

minute. Five cigarettes were smoked for each single determination. There was no appreciable change nor were the results more reliable when a larger number of cigarettes (up to fifty) were smoked. On the basis of the results obtained from this smoking experiment it was determined that the over-all effectiveness of two filters was not significant. One of these inadequate filters, in fact, permitted the passage of a higher content of nicotine than is noted in regular non-filtered cigarettes. One filter was quite effective in removing nicotine and tars. This, however, was closely packed, and a second filter of the same brand was less efficient as this subsequent experiment employed a filter of looser packing. The fraction of nicotine removed by the filter from the smoked portion of the cigarette is small in all instances. Twenty-one per cent of the total nicotine reaches the smoker in the use of a regular cigarette with no filter tip. It would seem, therefore, that the advertising claims of the various cigarette manufacturers are without a basis of fact.

BELL'S PALSY

Bell's palsy is a common disorder that may occur in persons of any age. This seventh nerve paralysis is usually of acute onset and is based upon edema of the seventh nerve, of its sheath, or of the periosteal tissues of the surrounding facial canal. Robinson and Moss[114] have reported the treatment of two patients with Bell's palsy using cortisone. Prompt recovery followed the oral administration of this hormonal agent. Definite improvement was noted in one patient three days after the institution of cortisone therapy. Within fourteen days the patient was completely recovered. Their second patient was a five-year-old boy with definite Bell's palsy. By the tenth day of therapy there was virtually no evidence of Bell's palsy, and the general physical condition of this patient was good. These authors continued the cortisone for a period of seven days following complete recovery, which they considered to be on the seventeenth day after the original institution of the treatment. Based upon this report by Robinson and Moss, this reviewer has reported a similar instance in one patient.[53] This patient had received both penicillin and anti-tetanis serum at the time of a minor injury. Three days after the administration of these preventive medications suspicious symptoms of minor reaction were noted. These cleared with the administration of cortisone by mouth. Several days later, however, typical symptoms of Bell's palsy were noted. The administration of cortisone in a dosage of 200 milligrams daily brought complete recovery in seven to ten days. The rapid recovery in comparison to previous reports of treatment of this condition would lead one to believe that the cortisone definitely had a beneficial effect upon the edema of the nerve or the sheath causing the seventh nerve paralysis.

The use of a double calcium and phosphate salt in the relief of allergic disorders has been reported by Kurtz.[71] No undesirable side effects nor any skin damage were noted with the use of a specially processed solution of calcium, glycerophosphate and calcium lactate. The preparation was

given subcutaneously, intramuscularly and intragluteally in rather massive dosages to nine patients. His results are reported to indicate a better therapeutic effect with this combination of calcium salts and phosphates than with single or double calcium salts used in the past.

What was once considered to be new drug therapy has now, after about eight or ten years, been accepted in such a common manner that few reports of antihistamines in treatment of allergic diseases are appearing in the literature. Most of the publications today concerning antihistamines deal with the introduction of a new preparation or one that provides prolonged or delayed action. Feinberg[40] feels that the major use of antihistaminic drugs is in the symptomatic treatment of allergic disease. He recognizes the close relationship existing between antihistaminic agents and local anesthetics. Proper allergic management using these preparations must be considered in the employment of these drugs as pure adjunctive therapy. He emphasizes the fact that asthma responds poorly to the use of these preparations. Swelling and inflammation may be uninfluenced, but the itching of acute urticaria is readily allayed. He denies previous reports that the addition of an antihistamine to penicillin will prevent a delayed reaction nor will these materials affect the reaction level. The proper dosage being the smallest amount that will afford relief is based upon the amount of sedation produced by each one. Their length of action also is a means of classifying the antihistaminic drugs.

When using I^{131} labeled proteins in immunologic investigation Dixon[34] takes two simple precautions to insure that the radioactive material really represents the originally labeled protein. First, the host must be prevented from using the $I.^{131}$ Second, in tracing the labeled protein, measurement of I^{131} should represent only the proteinbound radioactivity as indicated by trichloracetic acid precipitation. He feels that the most important application of this radioactive material in immunology is in the investigation of the dynamic *in vivo* aspects of immune reactions where sites of reaction and rates of degradation and elimination of antigens and antibodies are important.

LONG RANGE CARE

The long range care of allergic children has been the source of an interesting report by Rackemann.[108] He has noted the end results in a group of 688 children whom he had seen twenty years prior to this review. In this series, 25.8 per cent of the complaints were due to animal danders, 8.1 per cent to foods, 4.7 per cent to pollens and 43.3 per cent to mixed or unidentified causes. He has determined after twenty years that 138 of these patients could be called "cured." They were thought to be no longer sensitive to the substances which caused their original trouble. They were not under treatment at this time. Of the total, 28.4 per cent were still having trouble twenty years after they had originally been diagnosed and investigated. However, of this "poor" percentage, 11 per cent were con-

sidered to be moderately severe with only 2 per cent of the whole series requiring hospital treatment. He is of the impression that his 11 per cent unrelieved patients is too large a figure. He emphasizes that the results of any active treatment must be interpreted with caution because there is a strong tendency for allergic disease to subside by itself. In several of his asthmatic patients the complaints disappeared in the early twenties, and for a time the patient seemed quite well. Then, perhaps five, or even ten years later, the appearance of typical symptoms of seasonal hay fever were noted with no reappearance of bronchial asthma. Rackemann felt that this development indicated the basic lesion—the capacity to develop sensitiveness —was still present. In an attempt to explain this sequence, he is intrigued by the idea that certain foreign substances are better allergens than others. Therefore, they have a greater ability to excite allergic sensitiveness. Pollen sensitivity becomes of greater importance in later childhood. About one-fourth of all the children seen by this reporter began with eczema and asthma but developed hay fever in adult life.

A survey of fifty-nine cases of twins with allergic conditions existing in one or both is reported by Bowen.[14] In only seven instances were there true bilateral allergies of similar patterns. In fifty-two cases the allergic condition existed in only one twin. Bowen urges that twins be treated as distinctive individuals rather than permit dual costuming, wearing the same color of clothes, same tie and same jewelry. He encourages twins to dress independently and differently. He disagrees with the concept of maternal rejection as a cause of allergic conditions in children. In 85 per cent of his reported twins a familial incidence of allergy was present. He describes in detail three twins as examples of his principles.

Livingston and Harten[79] have demonstrated the absorption of antigen from the mammary ducts. The reaction tended to become more rapid as the amount of test antigen was increased. Traces of unaltered antigen were absorbed rapidly from the mammary ducts of both normal and diseased breasts in human beings. They state that the mammary ducts should be considered as possible sites for the absorption of allergenic substances introduced for treatment or diagnostic purposes.

Susceptibility or resistance to mumps may be determined by the reaction to a skin test with mumps antigen. Cabasso and Hoagland[20] have described the results of testing twenty-three subjects. The antigen employed was made from infected allantoic fluid. An erythema of 10 mm or less is considered as a negative response, with erythema of 11 to 15 mm being doubtful. Over 15 mm is recorded as a positive reading. This positive reaction usually develops several months after the onset of the disease.

ALLERGIC CHILDREN

Environmental changes, trial diets and the removal of foci of infection are important procedures in the management of the allergic child accord-

ing to Criep.[29] No child is too young, in his opinion, to receive prophylactic pollen therapy for seasonal hay fever. He emphasizes the importance for the physician to avoid confusing asthma with pancreatic fibrosis, congential laryngeal stridor, tuberculosis, croup, Loeffler's syndrome or foreign bodies in the lungs. This author also outlines general measures that should be followed in the management of the infant with severe atopic dermatitis. That it may be possible to reduce the incidence of major allergic syndromes is the contention of Glaser and Johnstone.[50] It was the purpose of their study to determine whether completely withholding cows' milk from the diet of potentially allergic newborn infants through the early months of life would influence the development of major and minor allergic diseases. In their group of ninety-six infants, eighty-eight were given soybean milk, three were exclusively breast fed and five were given meat base formulas. The histories of seventy siblings of infants in the experimental group were reviewed as a control. Sixty-five were included in the control group since five could not be followed for a sufficiently long period of time. In their results fourteen of the experimental group had shown major allergic diseases compared with forty-two of the sibling control group and ninety-one of a non-related control group followed to comparable ages. They decry the administration of cows' milk as a trial formula in a potentially allergic newborn infant. It will be interesting to see whether the ideas offered by these writers meet with the general approval of the average pediatrician.

The prophylaxis of allergic disease is, as we have noted, an interest held by Johnston and Glaser. Their claim that withholding milk from the potentially allergic infant in the first few months not only prevents sensitization to milk but also prevents sensitization to other allergens is the subject of an editorial.[39] It is doubtful if this theory will find ready acceptance by most allergists or pediatricians. The writer editorializes that a newly born infant, fed upon soy bean food can be exposed to some hazards. This procedure has the possibility of doing more harm than good. Diarrhea and sore buttocks that result in some infants are not matters to be passed over lightly. This reviewer follows the conservative line. It is my belief that it is not necessary to completely eliminate milk from the diet of an infant unless there is a definite clinical indication for this procedure.

Ratner and Silberman[109] are not satisfied that available data demonstrate that the capacity to become sensitized is controlled by genetic influences. In their study of 250 children and their families there was no relation between the type of family history and the age of the onset of symptoms. A careful review of their study and inquiry over a period of fifteen years indicated an extremely low incidence of familial trends in allergic disease. They conclude with the thought that no genetic hypothesis can be made to fit the existing rate as regards allergic disease. An editorial[36] raises the question of how many physicians will agree or disagree with the

hereditary concepts brought forth by Ratner and Silberman. The proof of heredity in allergy has been weakened apparently by the failure of those believing in the hereditary factors to agree whether it is a Mendelian dominant, a recessive or intermediate. The editor believes that the published evidence of these authors falls short of conclusive proof and hopes that the recognition of this fact may be a stimulus to further study of the available data.

DRUG SENSITIVITY

This reviewer has been impressed during the past year with the recognition that drugs and drug sensitivity have been receiving. Not only is this true as regards the incidence of recorded penicillin reactions, but it is also noticeable in published findings of the part played by drug sensitivity in the production of serious and often fatal allergic reactions. It must be remembered that any drug is capable of producing an allergic reaction, and every patient is potentially sensitive to drugs. The frequency with which medication is administered by a physician and the regularity with which a patient will use self-suggested drugs are probably two large reasons for the increased incidence of drug allergy.

Brown[16] has provided an inclusive drug review in a special article. He has supplied to the specialist an index of those drugs most frequently causing allergic reactions. He stresses the point that a drug with a single action is yet to be discovered. Similarly, the patient with a single reaction has yet to be born. This reviewer has found this complete work of Brown to be most valuable. It can be highly recommended to the general practitioner and to the specialist in allergy. The manuscript has been used in my office for reference and for review on innumerable occasions. It is the moral duty of every physician to be cognizant of the effects of drug allergy. Brown has arranged in alphabetical order the drugs most likely to cause allergic reactions. He describes under each heading the types of reactions most commonly noted. To make the review doubly useful, the drugs commonly known to cause blood and skin reactions are listed separately from the alphabetized index. Lowell[80] believes that all physicians should be familiar with the principal features of allergic reactions. They should understand those factors which are known to promote the development of allergy and also to have clearly in mind the means to be taken in order that allergic reactions may be avoided. It must be remembered that allergy to a drug does not occur spontaneously but must follow exposure to the preparation. In most instances this exposure precedes the appearance of allergic symptoms by five to twenty-one days or longer. Allergic manifestations usually recede two to three days after discontinuation of the drug. It is noted that allergic signs and symptoms usually clear promptly upon withdrawal of the responsible drug except in the familiar example of allergy to penicillin. Here the symptoms may continue to be present for several months after the anti-

biotic has been discontinued. In agreement with other writers, Lowell feels that the skin test as a means of determining sensitivity for drugs is of no appreciable value. He has divided the drug reactions into four categories. These are actually divisions as to severity of complaints. Category one comprises those reactions characterized by generalized urticaria, edema, rhinitis and circulatory collapse. Category two includes those reactions of erythema, rash—with or without itching—and fever. Category three describes those symptoms resulting from topical application of a drug which results in contact type of allergy. Category four includes those reactions which are of such potential danger to the patient that further administration of the causative drug is clearly contraindicated. These include the anemias, severe leukopenia, agranulocytosis, exfoliative dermatitis, nephritis and those reactions associated with diffuse changes in the blood vessels and connective tissue. In treatment of drug sensitivity the use of epinephrine 1-1000 has no substitute. To stop the administration of the drug is the first step in treating the types of allergic reactions that are not associated with collapse. Excretion of the drug is enhanced by giving fluids by mouth or parenterally in order to bring about diuresis. Whole blood transfusions should be used in these instances of hypoplasia.

BONE MARROW EFFECTS

The influence of drugs on the blood and bone marrow has been adequately described by Heck.[56] When a drug shows definite toxic properties, it should be excluded from the therapeutic program if there are available drugs possessing the same action. Blood and bone marrow reactions may be evidenced in a single element, in all elements or in various cellular combinations. The end result of the sudden or vague response may be either reversible or irreversible upon withdrawal of the offending drug. Granulocytopenia is initiated with an acute onset, chills, sore throat, aching in bones and a leukopenia with decrease or disappearance of neutrophiles. Various form of treatment have had no specific effect on the bone marrow. Antibiotics do offer protection even though no progress has been accomplished in the stimulation of myeloid cells in the marrow. Among the foremost offenders in the production of blood and bone marrow changes are aminopyrine, sulfonamids and phenylbutazone (Butazoilidine). In essential thrombocytopenic purpura it is imperative that careful inquiry be made regarding drug ingestion. Hemolytic anemia may appear acutely or the reaction may have a gradual onset with a long chronic course. With the presence of an enlarged spleen, the diagnostician must consider leukemia as a definite diagnosis, although leukemia-like pictures may result from drug ingestion. The highest mortality rate in bone marrow affectation is noted in aplastic anemia. The general effect upon the bone marrow is associated with fatigue and weakness

or with purpuric manifestations. The diagnosis cannot be made by the peripheral blood picture but rests with the bone marrow. Drug induced hypoplastic syndromes differ from other hypoplastic syndromes in that the disease develops in only a small proportion of the population exposed to risk. The severity of the hypoplasia shows little relationship to the dose of the drug administered.

Osgood[97] states that there is a difference or idiosyncrasy to the particular drug in the response of the person affected. The mechanism of this problem is unknown. Osgood feels that the drug or one of its metabolites, in susceptible persons, combines with an essential protein of the cell to form a new protein that eventually causes the development of antibodies. The drugs most commonly known to produce such an idiosyncrasy are anti-convulsants (Mesantoin), antihistaminics (Phenergan), antimicrobial agents (arsenobenzols and chloramycetin), antithyroid agents (thiouracil), sedatives (sedormid and aminophyrine), spasmolitics (phenothiazines) and an unclassified group containing gold preparations, phenobutazone and nitrophenols. Other drugs may produce this hypoplastic anemia, but the estimated relative risk is either low or exceedingly rare. Complete aplasia almost never occurs. Determinations of hemoglobin concentration, leukocyte count, reticulocyte count and clot retraction time serve as a basis for comparison with subsequent blood studies after therapy has been started. Patients with asymptomatic granulocytic hypoplasia should receive a daily dosage of 300,000 units of penicillin with 0.5 grams of streptomycin given intramuscularly. Therapy should be given twice daily in severe hypoplasia and supplemented in forty-eight hours with 500,000 units of penicillin G given intramuscularly. This dosage of penicillin should be doubled every forty-eight hours until rapid improvement is apparent. It is seen, therefore, that the strong use of antibiotic therapy is indicated as an initial step in the correction or control of hypoplasia due to drug idiosyncrasy or sensitivity. Fresh whole blood transfusions given every six hours comprise the only effective therapy for thrombocytic hypoplasia. These transfusions should be repeated as often as necessary to maintain some clot retraction. Osgood[98] believes that the therapy of hypolastic syndromes due to drug idiosyncrasy is initiated with stopping the drug immediately. For thrombocytic hypoplasias blood transfusions using fresh blood not over six hours old should be given as often as necessary to keep some clot retraction at one hour. In the treatment of granulocytic hypoplasias, the administration of procaine penicillin, 300,000 units and streptomycin, 0.5 grams twice daily with added penicillin G is advised if the fever is not controlled. If the hemoglobin drops below 8 grams in erythrocytic hypoplasias, blood transfusions are a necessity. The use of cortisone or ACTH in full doses is definitely worth an adequate trial. There are no known substitutes for fresh blood transfusions and antibiotics in the correction of drug-induced hypoplastic anemias.

PROCAINE SENSITIVITY

Efocaine is a solution of 1 per cent procaine, .25 per cent procaine hydrochloride and 5 per cent butyl-P-aminobenzoate in a solvent composed of 2 per cent polyethylene glycol-300, 78 propylene glycol, and water. In the past it has been felt that this is a safe local anesthetic agent which contains a prolonged action. Recently, however, clinical evidence would tend to indicate that this drug has not met one vital requirement, i.e., safety. Angerer, Su and Head[4] issue a case report in which the attention of the reader is called to the first known death attributed to the use of efocaine. Other severe complications have been transverse myelitis, toxic neuritis and less severe reactions such as perirectal sloughs, post-injection pain and atonic bladders. Their patient died as a result of an intercostal injection of efocaine. They advise against the use of this preparation for local anesthesia, especially in a region near a vital organ such as the spinal cord. That anaphylactic death can result from the administration of procaine hydrochloride is the basis of a report by Criep and Ribeiro.[30] It is always well to call attention to severe or fatal reactions from a drug that is thought to be comparatively safe. On some rare occasions, serious, unexpected side-effects may occur. Reactions to local anesthetic drugs such as procaine may be divided into those upon a toxic basis and those which are characterized by allergic symptoms. It must be remembered that skin tests are of no diagnostic value in determining sensitivity to a drug such as procaine since this material is not of a protein nature. Criep and Ribeiro recommend that prior to the use of procaine, cocaine and related drugs one should apply them with an applicator intranasally. If sensitivity is present to a marked degree, untoward symptoms will develop within a few minutes. If the reaction appears negative by this means of testing, then the administrator should feel comparatively safe in giving the drug to that particular patient.

Severe or fatal side reactions have been noted recently to occur with the use of procaine amide hydrochloride. These untoward reactions have been characterized by blood changes, ventricular fibrillation or acceleration. Symptoms may be characteristically those of the usual allergic type reaction. Koffler[68] has reported a patient to whom 50 mg of procaine amide hydrochloride was administered orally. Within twenty minutes the pulse became regular and remained so for about two hours, after which time cardiac irregularity recurred but less frequently. Previous work with this preparation had demonstrated the suppression of premature ventricular contractions. In Koffler's patient, however, symptoms of generalized reaction—marked itching and edema—appeared within about twenty minutes. Amelioration of the allergic symptoms occurred in about one hour with the use of antihistaminic preparations. Procaine has been known to be concentrated seven or eight times more at the site of injured tissue than in other parts of the body. No trace of it can be found in the blood stream about twenty minutes after rapid intravenous

injection because of the rapidity with which it is broken down in the body. DeBold and Fox[33] report the administration of 1600 intravenous procaine treatments in patients suffering with arthritis. The material was given to 200 patients. Of the entire series, there were only three reactions with no other patients having been found sensitive to the drug. One of their patients had symptoms characteristic of bronchial asthma; their second patient complained of nausea, shortness of breath and generalized tremor; while their third patient complained of severe shortness of breath. All of their patients recovered approximately one hour after emergency measures had been employed.

VITAMIN AND DRUG SENSITIVITY

Harrison and Mercer[55] have reported an instance of vitamin A intoxication in a twenty-eight-month-old child. The diagnosis of such a condition can be made readily if the syndrome is kept in mind and if a careful history of vitamin intake is routinely taken. The principal clinical manifestations in this patient were hyperirritability, cheilosis, pruritus and swelling along the ulnas and along the fifth metatarsals. The diagnosis must be established upon three clinical factors, namely: a clear cut history of excessive vitamin A intake, elevated levels of vitamin A in the blood and roentgenographic evidence of subperiosteal new bone formation. Mothers of infants often feel that if vitamin intake is a necessity, then more vitamins would be of greater value. It has been estimated that the result of this rationalization is a daily use ten to twenty times the usual amount of vitamins A or D concentrate. The typical clinical picture usually results from over-dosage of vitamin A for a long period of time.

Sensitivity to aspirin and related drugs has been recognized by most allergists. Samter, Hall and Palicke[121] have studied a series of twenty-four patients sensitive to aspirin. They present evidence to substantiate their feeling that only acetylsalicyclic acid produces either asthma or angioedema. In the presentation of their paper it was stated that symptoms of aspirin sensitivity (characterized by wheezing, cough and respiratory difficulty) appeared three to four hours after the administration of the aspirin. In this reviewer's experience aspirin sensitivity is a sudden, alarming and intractable affair within a matter of seconds or minutes after the administration of the drug. True aspirin sensitivity in the asthmatic does not appear three to four hours after the administration of the drug but occurs practically as the medication is swallowed. Personal conversation with two or three allergists in attendance at this meeting revealed a feeling of disagreement with the authors in this regard.

There is a definite relationship between the chemical formulas of aminopyrine and phenyl-butazone. Many toxic manifestations have appeared from the use of the latter drug in the treatment of arthritis and allied rheumatic disorders. Nathan, Meitus, Capland and Lev[91] report a fatality which was thought to be due to overwhelming toxicity and possible hy-

persensitivity to this drug. The hypersensitivity signs and symptoms were related primarily to the skin and viscera. In spite of the cessation of the drug and the use of counter measures, the reported patient's clinical status continued to deteriorate, with ultimate death. Focal areas of infiltration of lymphoid cells in the adrenal cortex and medulla with degeneration of the cortical cells were determined at autopsy. The authors felt that this finding explained their failure to obtain any measure of improvement with the use of ACTH. They theorize that their results may have been somewhat improved had they used cortisone and/or adrenal cortical extract as substitution therapy.

Rapid dissolution of blood clots and fibrinous exudates has been obtained on many occasions, with the injection of streptokinase-streptodornase solution. These materials, being antigenic, permit the occurrence of dangerous anaphylactoid reaction especially when they are injected intrapleurally. Goehring and Grant[52] report a case of sensitivity to these enzymes. A subsequent skin test with the solution was strongly positive. This positive skin test reaction was determined five weeks after the intrapleural administration of the drug. As a result of their experience, they warn physicians to be on the alert for a possible anaphylactoid reaction due to streptokinase and streptodornase. Previous reports concerning the use of these materials have shown little reaction possibility from their use.

Sensitivity to mercurial derivatives used in the preservation of surgical catgut is the basis of a report by Rost.[118] Upon previous exposure to mercurial derivatives, generalized dermatitis had been noted by the patient about whom this report is made. In the process of an appendectomy (with care not to use mercurial skin preparation) medium chromic catgut was employed as a suture. Severe dermatitis appeared on the second postoperative day. Marked patch test sensitivity was demonstrated to phenol mercuric acetate, which was the solution contained in the catgut tubes. Control patch testing with the catgut itself was reported as non-reacting.

SERUM NEURITIS

Neuritis describes any process involving the peripheral neuron resulting in functional loss which may be sensory, motor or mixed. Garvey[48] states that the etiology of neuritis may be classified as virus, bacteriotoxic, deficiency, metabolic and chemical. In addition to these, antitetanic serum neuritis is felt to be more common than has been previously reported. The usual site for radicular lower motor neuron dysfunction is the shoulder girdle. The neuritis, however, may be multiple. Encephalitic features may overshadow the neuritic involvement and complicate the picture. When early, severe, localized or generalized radicular pain appears, suspicion of neuritis associated with serum sickness should be very strong. An accurate diagnosis may be delayed because pain may mask the paralytic features. Garvey feels that the treatment of the early stage of neuritis should be the same as that administered for the treatment of serum sickness.

Serum neuritis is less often recognized in the patient with serum sickness than are the typical symptoms of urticaria, arthralgia and elevated temperature. Watkins[151] describes serum neuritis as presenting itself with pain in the shoulders, and the affected muscles being those supplied by the cervical fifth and sixth roots. Weakness within a few hours or days after the administration of the serum has been noted. Residual weakness and apathy may be an eventual end result. Over a period of seven years this author has noted sixteen such instances of serum neuritis and highly recommends the substitution of tetanus toxoid in preference to the anti-tetanus serum.

PIROMEN

No significant changes in twenty-six patients receiving weekly subfebrile intravenous injections of Piromen were determined by Fond.[41] This report is in disagreement with some of the earlier articles on the use of this preparation but does seem to follow the trend of most reporters within recent months. Fond's initial dosage was 0.5 to 1 gamma. This was gradually increased up to a maximum of 5 gammas. Injections were given at weekly intervals. Two of the twenty-six patients stated that they did experience a mild degree of improvement in their symptoms. However, weekly determinations of maximum breathing capacity and vital capacity studies did not show any evidence of improved functional capacity. It is his impression that Piromen in subfebrile doses has no value in the treatment of bronchial asthma. McCorriston[81] has evaluated the therapeutic response in various dermatoses to Piromen. Best results were obtained with this preparation in the allergic eczematous group. Clinical improvement was more rapid when Piromen was instituted early in the course of their complaints. The majority of patients studied in this report were complaining of atopic dermatitis. Thirty-seven of the 100 patients in this investigation were of this diagnosis. This author considered the material to be relatively safe and to be a good adjuvant to other forms of therapy.

HORMONAL ALLERGY

Though skin tests may be of some help in detecting hormonal allergy; Wolf, Bailey and Coleman[156] feel that no degree of reliance can be placed upon this procedure. Endogenous allergy is exemplified by sympathetic ophthalmia and paroxysmal hemoglobinuria. The size of the skin test reaction could not be correlated with good or bad results in treatment. These authors feel that some instances of pre-menstrual tension, headache, pelvic pain and skin disturbances may be due to the patients' sensitivity to their own hormones. Those patients which were selected for desensitization were generally those with positive histories of allergy, in whom hormonal or other treatment had failed to relieve their presented symptoms. Skin tests on 117 women patients were done with twenty of these showing 2+ reactions to one or more hormone solutions in twenty-four hours.

Forty-seven patients showed smaller reactions. Materials used for skin testing consisted of controls, estradiol, estrone, percorten, progesteron, pregnanediol, testosterone, insulin and Synapoidin. Of the twenty-six patients eventually treated by measures of desensitization, complete relief was obtained by six and partial relief was secured by four additional patients.

ANTIBIOTIC SENSITIVITY

Anaphylactoid reactions attributable to penicillin and streptomycin are the subject of an editorial.[37] A recent survey by H. Welch and co-workers[153] gives information of sixty-three cases of severe anaphylactoid shock. Of these, nineteen were fatalities. Four reactions could be attributed to streptomycin. Three of these reactions were after intrathecal injections. Eighteen of the fatalities were due to penicillin sensitivity. In only one instance was the drug given by mouth with the remainder given intramuscularly. Chloramphenicol, aureomycin and terramycin are given primarily by mouth. It was interesting to note that none of these mentioned antibiotics produced any anaphylactoid reactions. Neo-Penil was responsible for five deaths in a total of twenty-five severe reactions of the anaphylactoid type. Particular importance was stressed by the editor to the fact that twelve of eighty-eight patients had demonstrated previous evidence of sensitivity. Twenty-six of these eighty-eight had a history of major allergic findings. It was estimated that a great risk is taken in giving a parenteral antibiotic to a known allergic patient.

The clinical course and skin testing suggested penicillin to be the etiologic agent in a case of Loeffler's pneumonia developing subsequent to a course of penicillin therapy. The case report by Reichlin, Loveless and Kane[113] demonstrates the production of marked pulmonary infiltration and eosinophilia. Their patient, under treatment for syphilis, had received a few injections of procaine penicillin in sesame oil and had had mild reactions which were well controlled with antihistaminic preparations. However, on about the seventh injection, he developed severe burning and soreness in the throat, cough, chills and fever with throbbing headache. He was admitted to the hospital where subsequent physical and laboratory examinations confirmed the diagnosis of Loeffler's syndrome. Positive intradermal testing was determined during the time that the patient was showing decided eosinophilia. Subsequent testing when the patient was well controlled revealed negative reactions. It was thought that negative tests with procaine penicillin were recorded as such because of the restraining vascular influence of the procaine.

Crissey and Caccamice[31] have observed skin reactions with the use of five of the most widely employed antibiotic preparations. Dermatologic manifestations of penicillin sensitivity may be expressed as urticaria and edema which are the primary serum sickness types of reactions. Other dermatologic evidence of penicillin sensitivity can be seen with vesicular

phytid reactions and exfoliative dermatitis. Serum sickness type of penicillin sensitivity occurred in 6 per cent of the patients observed by these writers. They have remarked that oral penicillin has a very low incidence of side reactions. This reviewer is in complete agreement with their feelings on this subject. They considered that the primary treatment for any form of penicillin sensitivity regardless of severity is to stop the drug. In the serum sickness type of reaction, prolonged use of antihistaminic preparations is strongly advised. They also recommend the use of epinephrine 1-1000 as well as the administration of ACTH and cortisone. Following the use of streptomycin, these authors observed the presence of maculopapular eruptions, toxic erythema, exfoliative dermatitis, urticaria, purpura, erythema nodosum and erythema multiforme. Because of the high incidence of crossed reactions, substitution of the dihydostreptomycin form of this particular antibiotic is considered to be useless. With the employment of chloramphenicol, skin reactions were not very commonly noted. With this preparation, oral complications and anorectal vaginal reactions are more frequent. Fixed drug eruptions, urticaria, photosensitization and dermatitis at the groin and scrotum may be seen with the use of aureomycin. Skin reactions to terramycin are, in general, quite rare. Therapy of this problem is usually discontinuation of the drug with good relief.

The most commonly encountered side-effect from oral terramycin was anorexia. This was the experience of Miller and Walker.[87] Seventy per cent of their seventy tuberculosis patients receiving 5 grams daily for four months noticed this side-effect. Nausea was experienced by 50 per cent of the patients with vomiting occurring in only nine individuals. During this period of observation these patients also received 2 grams of streptomycin every third day. From neither preparation was there any dermatologic or hematologic complication.

Statistically significant difference in untoward reactions following use of aureomycin and procaine penicillin troches has been reported by Kutscher et al.[72] Reactions to aureomycin troches were observed in fifty-one of 100 patients treated. Of these, fourteen patients were forced to discontinue the therapy because of the severity of the reaction. Thirty-eight per cent of the 100 patients did respond in an allergic way to the use of procaine penicillin G troches. Eleven patients were forced to discontinue the medication because of the severity of their reactions. Control studies showed that seven of the fifty patients receiving aureomycin medicated troches complained of reaction upon receiving placebo troches. Seven of the fifty patients who received placebo troches in the penicillin group also showed some evidence of reaction. The authors believe that antibiotic troche medication is not indicated for promiscuous use because of the high incidence of local reaction.

Marked sensitivity to phenobarbital has been cited by McGeachy and Bloomer.[82] Fever, mental confusion and toxic damage of vital organs with an erythematous rash were noted in one female and two male

patients. There were two deaths in this series of three patients with ingestion of therapeutic doses. Necropsy studies in one patient demonstrated hemorrhages in the trachiobronchial tree, skin, stomach and oral cavity. The kidneys were also involved, and the spleen was congested. All stages of cellular necrosis were noted upon microscopic examination of the liver. The presence of the phenol group in the causative drug was considered to be significant. The diffuse cellular damage was thought to be due to the liberation of a phenol derivative. Procaine hydrochloride by intravenous route was thought to be the factor permitting one of the three patients to survive the severe reaction. This surviving patient also presented rash, swollen painful joints and elevated temperature which were aggravated by the oral administration of pyribenzamine. Since these patients showed some tendency to bleed, the authors postulate that hypoprothrombinemia may be a factor. A valuable therapeutic material may be vitamin K.

A comparison between true drug sensitivity and drug irritation in the eye has been the subject of an interesting paper by Theodore.[139] Itching dermatitis, catarrhal conjunctivitis and conjunctival eosinophilia or basophilia are the characteristics of drug sensitivity in contact allergy around the eye. Drug irritants, on the other hand, cause their reactions by direct conjunctival irritation. The alkaloids, especially the miotics, and related compounds are particularly apt to be included in this irritating group. A non-specific, watery conjunctivitis without dermatitis or eosinophilia is the clinical picture of irritative conjunctivitis due to drugs. The use of properly prepared solutions of the drug which has caused an irritation will be a source of relief to these patients if the drug has to be continued. Drug allergy requires substitution of a different preparation. It is, therefore, important to make a definite distinction between true sensitivity and drug irritation. As post-operative therapy for an appendectomy, a patient received intravenous 10 per cent dextrose. O'Hara, Shapiro and Creeden[95] observed their patient to have a chill, markedly elevated temperature (106°F) and a fall in blood pressure to 60 systolic with no diastolic during the administration of the second 1000 cc of intravenous fluid. Necropsy studies demonstrated an allergic type of bronchitis with secondary widespread atelectasis. Culture of the heart blood and the spleen showed Aerobacter aerogenes. The authors feel that a generalized anaphylactic reaction resulted from the responsible organism being present in the bottle of solution.

Nikishin[93] has reviewed five instances of anaphylactic reactions to penicillin which were obtained from the literature. No previous signs of sensitivity had been experienced with penicillin administration in these individuals. Immediate anaphylactic reaction was introduced with choking, wheezing, substernal oppression, circulatory collapse and profuse perspiration. Since the duration of drug allergy is highly unpredictable, the author emphasized the need for discrimination in the use of penicillin

to prevent severe or fatal anaphylactic shock. The appearance of the L.E. factor in the plasma and L.E. cells in the bone marrow of three patients with penicillin reaction has been reported by Walsh and Zimmerman.[150] The patients showing the appearance of these unusual features had rather severe serum sickness type reaction associated with marked skin lesions. This finding would suggest that the L.E. phenomenon may have some relationship to hypersensitivity and may be seen in conditions other than systemic lupus erythematosus. It is necessary to screen persons with previous histories of penicillin reaction in order to prevent further or more severe anaphylactoid pictures. Sohval[128] states that it is necessary to select carefully patients for penicillin administration in view of the immediate constitutional reactions that may occur. It is also necessary to be extremely careful regarding the injection of the medication in order to avoid entry of the penicillin into the blood stream. Collins-Williams and Vincent[27] agree with most pediatricians that reactions to penicillin are rare in children. They have reviewed the records of the Hospital for Sick Children in Toronto, Canada, and were able to find only three cases of known sensitivity for this drug. In allergic children, however, it is not rare as evidenced by their 6 per cent of penicillin reactions in private allergic patients. They are of the opinion that skin testing had little value in the evaluation of penicillin sensitivity. Two hundred children were tested by scratch and intracutaneous methods. Two-thirds of this group were non-allergic children and one-third was considered allergic. Sixty-eight of the non-allergic group had received penicillin previously with thirty-three receiving it for the first time when the skin test was performed. Thirty-two of this same group had not received it previously. For the group of allergic children, similar figures were fifty-three, one and thirteen, respectively. No reactions to penicillin by scatch test were determined, but three did show positive reactions by intracutaneous test. They believe that the question of penicillin sensitivity is complicated by the different types of penicillin available. Whether or not a patient will react to penicillin G after having shown some sensitivity to penicillin O is open to question. There is a distinct doubt as to whether there is a specificity to the different types of penicillin. They feel that the low incidence of reactions in non-allergic children should not lull the average physician into a false sense of security. Some of the sensitivity reactions in children are quite severe with one fatality having been already reported in the literature. The drug should be used orally in children if possible. Intramuscular use should be reserved for those patients with vomiting or for those individuals with very acute illnesses. In the allergic group that was skin tested a high incidence of concurrent mold sensitivity was noted. The authors could determine no correlation, however, between a postive skin test with penicillin and those with the penicillium group of molds. They emphasize that a positive skin test probably indicates sensitivity, but a negative skin test with penicillin does not mean a true lack of sensitivity.

Wofford[155] reports an unusual instance of anaphylaxis to penicillin associated with a ruptured tubal pregnancy. His patient was a young, white, married woman admitted to the hospital because of severe circulatory collapse. She had previously received 300,000 units of penicillin. Within three or four minutes after the administration, violent sneezing, severe pelvic pain, shock and collapse were noted. Though there was no asthma, massive edema of both lips and generalized circulatory collapse were noted. Her abdomen was soft, but in view of the pelvic pain and the absence of menstrual periods during the previous four months, a ruptured ectopic pregnancy was considered. Emergency medical care gave good relief from her symptoms of reaction. Three days following her hospital discharge she was re-admitted for a laparotomy. This surgical procedure revealed a ruptured left tubal pregnancy. Wofford is of the opinion that his patient differs from other reported cases in that an ectopic pregnancy complicated the picture. He felt that it was more than mere coincidence that her tubal pregnancy would rupture within five days of her penicillin reaction. It was his impression that some alteration in the circulatory supply of the fallopian tube, brought on by the shock, hastened the rupture of this pregnancy. The immediate circulatory collapse, however, was not considered to be due to the ectopic pregnancy.

The history of each patient about to receive penicillin therapy should include a question concerning their past experience after using this drug. Mayer et al.[85] advised skin testing with a high dilution of penicillin prior to the administration of this drug to those patients presenting a positive or questionable history of sensitivity. They believe that the positive immediate skin test to this preparation contraindicates the use of the drug, or it must be given as a calculated risk warranted by the seriousness of the illness. Three illustrative cases of anaphylactoid shock following penicillin therapy and bronchial asthma have been reported by Sterling.[132] Sensitivity for penicillin may take place from previous oral use or when repeated injections have to be given daily for prolonged periods. Sterling is doubtful if anaphylactic shock to penicillin occurs at the first injection. Considering the amount of penicillin used in medicine today, anaphylactic shock reactions are extremely uncommon according to this author. He considers the five cardinal symptoms of impending anaphylaxis to be syncope, burning or heat throughout the body, local, or generalized pruritus never before present, choking sensation in the throat and severe paroxysmal pain varying in location. He describes nine cases and reports three of these in complete detail. Penicillin G or procaine penicillin was used in all nine patients. He agrees with other writers that skin testing patients suspected of penicillin sensitivity is an unreliable guide as an indication of true sensitivity. Edema of the uvula after using penicillin powder by inhalation is not a contraindication to the administration of the drug by intramuscular route.

Siegal, Steinhardt and Gerber[124] report that penicillin anaphylaxis is

on the increase. Chemotherapy should be avoided altogether for the therapy of minor respiratory infections which are mostly viral in nature. They recommend an accurate history to be taken both as to personal and family history of allergy before administering or prescribing penicillin. If a patient has never been exposed to penicillin in the past, the danger of anaphylactic shock is negligible. In evaluating the history of previous penicillin allergy the physician should distinguish between a delayed or immediate reaction. He avoids the use of penicillin in the treatment of any patient who has a contact history of penicillin. These individuals may react in a dangerous manner. They emphasize that the absence of any previous allergic reaction to the drug does not preclude the possibility of anaphylactic sensitization. They call for greater caution in the use of this particular antibiotic.

The panel discussion on allergic reactions to penicillin edited by Schiller[122] is highly recommended to every physician. Sherman[123] emphasizes that a negative reaction to the scratch test or intracutaneous test is never a reliable index that the patient is not sensitive to penicillin. This does not indicate that he will not have an immediate reaction or that a delayed reaction will not eventually follow. Rose[116] advises that penicillin should be used carefully and wisely since it is one of the most useful antibiotics at our disposal. For immediate therapy of the near fatal shock, he advises the intravenous administration of hydrocortone. This compound, 100 mg in 100 ml of 5 per cent dextrose, acts quickly and, according to Rose, is the most rapid acting of all hormone preparations. Blanton and Blanton[10] report on an unusual penicillin hypersensitiveness. Their patient possessed such extreme sensitivity that severe paroxysmal dyspnea was experienced by rather distant association with penicillin aerosol. They indicate that patch testing with graduated dilutions of penicillin may serve as immediate warning of danger in the oral or parenteral use of the drug. Most of the authors, however, reporting upon penicillin sensitivity find that patch, scratch or intracutaneous testing is of no value in the determination of sensitiveness for penicillin. Weiss[152] reports an incident of anaphylactic reaction following the antral inhalation of penicillin. He emphasizes that language clearly understandable to the patient should be used in questioning such individuals regarding their reactions or sensitivity to previously administered penicillin.

Larsen[74] calls attention to the possibility of severe anaphylactic reaction occurring immediately following penicillin administration. He describes two instances in which both patients had previously received penicillin without unpleasant reaction. The reported instances were sudden in onset, alarming in their severity and fortunately responsive to emergency measures. Beck[7] says that there are four courses possible in the treatment of a penicillin sensitive patient with a serious illness. These four courses are: the administration of penicillin regardless of the risk, the attempted desensitization to penicillin, the use of other antibiotics with less likeli-

hood of a successful outcome or the administration of penicillin along with a substance such as antihistamine or cortisone in an effort to obviate reactions. He reports upon a patient with sub-acute bacterial endocarditis in whom other antibiotics were not successful, but the administration of penicillin with Chlor-trimeton or cortisone was successful. The combination of penicillin and the antihistamine was 1,000,000 units of antibiotic with 10 mg of the antihistamine per injection. Brown et al.[18] cite three cases of fatal fungus infection associated with antibiotic therapy. In the treatment of their patients, more than one antibiotic was used. Since the disease increased after the introduction of broad spectrum antibiotics, they consider that the danger of moniliasis might be due to the use of aureomycin, chloramphenicol and oxytetracyline.

In an effort to determine the circulation time in their patient, sodium dehydrocholate was given intravenously by Coggins, Skinner and Burrell.[24] Immediate dyspnea, cyanosis, profuse perspiration and a rapid weak pulse were noted. A marked drop in blood pressure and evident circulatory collapse were immediate. Eventual death occurred on the eighth hospital day in spite of heroic measures of therapy. Though such reactions are rare, the authors state that sodium dehydrocholate should not be used routinely for the determination of circulation times. They advised the use of calcium gluconate as a substitute measure. They warn, however, that calcium gluconate may be contraindicated in those patients who have received digitalis or one of its glucosides.

Herrell[58] joins those who feel that the indiscriminate use of antibiotics is a most unfortunate occurrence. Toxicity involving the eighth cranial nerve is by far the most important reaction that may accompany or follow streptomycin therapy. Herrell believes that little distress, however, will be encountered if the dosage and the matter of renal function concerns the physician giving this drug. He warns against the promiscuous use of chloramphenicol. He believes that this drug should be used with extreme caution because it is a synthetically prepared nitrophenol compound, and its use may be associated with suppression of the bone marrow. Berkowitz et al.[8] have found in their survey that penicillin is used almost as freely as aspirin. In the over-all group of drugs under study, a higher incidence of reaction was noted in allergic children than in non-allergic children. In the former group, 20 per cent reactions were found. In the latter group the reactions were 2.4 per cent which represented an eightfold difference. Because of the marked incidence of "side-effects" with the use of phenobarbital and aureomycin, the authors report that these really represent, in most instances, minor allergic reactions.

INSECT ALLERGY

Mueller and Hill[89] find that severe reactions to the stings of bees and wasps seem to be increasing. These patients, however, can be desensitized. If the insect that stung the patient cannot be positively identified, they

recommend the use of a mixed desensitizing extract. This mixture should contain bee, paper wasp and yellow jacket antigens. Symptoms of allergic rhinitis and asthma from contact with locusts has been reported by Frankland.[43] Of thirty-four workers investigated, four produced the above symptoms. Fourteen others of these workers had a sub-clinical sensitivity as evidenced by positive skin tests with locust extract. Inhalant allergic symptoms responded quite successfully to specific hyposensitization. The appearance of symptoms upon exposure to locusts is more likely to appear in allergic patients than in so-called normal individuals. Pain and muscle spasm are the main systemic manifestations of the black widow spider bite as reported by Allen.[3] The muscles of the abdomen and back are most commonly affected in this illness. The site of damaging action is on the nerve endings with the venom stated to be a toxalbumin. No permanent neurologic damage has been reported. The use of curare is reported by this author to have been immediately successful in alleviating the severe signs and symptoms. Cohen[25] believes that the muscular spasms, tension and increased reflexes of a patient bitten by the black widow spider suggests an abnormal activation of acetylcholine. In some instances death may follow the bite, but this event is rare. The usual acute symptoms persist from twelve to twenty-four hours, but the muscular tenderness and cramping may persist for as long as one or two weeks. Administration of cortisone to his patient gave good relief, with injections being in a dosage of 50 mg at four-hour intervals. Calcium glucose and procaine hydrochloride had been given without apparent relief. His second patient was given ACTH with marked relief and no further symptoms being noted after thirty minutes. He considers these two hormonal agents to be the drugs of choice in the treatment of black widow spider bite reaction.

Papular urticaria is now considered to be upon a basis of parasitic sensitivity rather than to food allergy. Rook and Frain-Bell[115] noted good improvement upon hospitalizing their patients. The suggestion was made that the flea or bed bug had been removed from the environment of the sensitive patient. They discuss in interesting fashion the long history of the human flea. No benefits were derived from antihistaminic preparations in papular urticaria.

RESPIRATORY-CARDIAC ASTHMA

Meakins[86] has stated that "cardiac asthma" is a misnomer. The proper term to be employed is "paroxysmal cardiac dyspnea." In true bronchial asthma, dyspnea does not occur in free periods unless it is associated with respiratory disturbances. Dyspnea between paroxysms with relation to physical exertion is characteristic of "cardiac asthma." Increased pulmonary venous pressure is a fundamental requirement for paroxysmal cardiac dyspnea. Correct diagnosis and treatment are based upon this concept. Dyspnea due to cardiac disturbances is somewhat individual in

that the respiratory movements are rapid, shallow and non-obstructive. The basal râles determined on physical examination are caused by edema of the pulmonary organ and not by mucous secretion. Vital capacity recordings show a definite reduction at all times whether or not the patient is having active symptoms. Circulation time is prolonged in cardiac failure and normal in bronchial asthma. Mitrovalvular disease (stenosis) and hypertension with left-sided failure are two major factors in the production of cardiac dyspnea. Other causes are aortic stenosis and left ventricular failure due to mild cardio-infarction. Oxygen inhalation for the relief of attacks and maintained digitalis dosage for prolonged symptoms are requirements that cannot be overlooked.

CHILDHOOD ASTHMA

That bacterial sensitization is a common cause of childhood asthma is the consensus in answer to a question concerning this problem. Ratner[110] believes that the subject is open to question, in that an individual may be hypersensitive to bacteria and again a bacterial infection may be superimposed upon allergic tissues. The most important diagnostic means for differentiation between allergic and infectious processes is nasal secretion examination. Rosen[117] believes that bacterial infection is an important, common cause of asthma in children. He uses antibiotics combined with injections of bacterial antigen for practical treatment. He finds his greatest problem in determining whether the so-called cold in these children is a bacterial or viral infection or a simple allergic rhinitis. Kahn,[62] on the other hand, does not believe that asthma due to bacterial sensitization per se does exist. In an effort to explain the prolongation of ragweed asthma after the official end of the season, he is of the opinion that there is sufficient air-borne pollen to provoke ragweed asthma under the nonspecific stimulation of an acute cold. Then, too, there may be a sufficient storage of ragweed antigen in the anatomy for several weeks to provoke bronchial asthmatic complaints.

Bacterial allergy is of the greatest importance in children and may simulate any allergic syndrome, in the opinion of Chobot.[22] He found that infection was the sole cause of asthma in 30 per cent of his patients. In 87 per cent of his patients infection was a factor, though combined with inhalant or food sensitivity. As a cause of asthma in children, he ranks infection first with inhalant sensitivity second and food allergy third. There is no definite evidence of true bacterial asthma unless one will accept the rare occurrence of asthma from a dose of vaccine. Thus, Holman[60] believes that patients whose bronchial asthma is associated with an infectious head or chest cold can be found sensitive to allergens, the treatment of which is frequently successful. He considers a cold to be only one of a number of accessory factors. Glaser[51] is of the opinion that children who have recurrent upper respiratory infections complicated by asthma should receive a complete allergy study. He does not rely upon

antihistaminic or antibacterial drugs alone because they represent only symptomatic and not specific therapy.

TRYPTAR

Trypsin is a naturally occurring body enzyme. This was administered in aerosol form to seventy-three patients with respiratory conditions. These patients were under the care of Unger and Unger[145] who found that the therapy was non-toxic. It did not affect living tissue, but at the same time the viscosity of the sputum was definitely lessened. Their initial dosage is 75,000 units dissolved in 1.5 cc of the aerosol trypsin diluent. The first follow-up dose consists of 100,000 units in 2 cc of the diluent with subsequent increases to 125,000 units in 2.5 to 3 cc of the diluent. A very satisfactory concentration for clinical results proved to be 50,000 units of trypsin dissolved in each cc of the diluent. Before each inhalation, the patient is usually given .25 cc of 1-1000 solution of epinephrine combined with .75 cc of a soluble histamine. The results were comparatively good in infectious bronchitis or pneumonitis; but in those patients with bronchial asthma, the response was not in the same dramatic fashion. Mediocre effects obtained with the use of the enzyme in chronic bronchial asthma were somewhat improved in patients with emphysema. In a subsequent publication[146] the same authors report better results in paroxysmal bronchial asthma. When the bronchial asthma was complicated by infectious bronchitis, pneumonitis or bronchiectasis, the results were quite startling. Transient hoarseness was thought to be due to larger doses and too rapid administration. When the inhalations were given more slowly and in smaller doses, the hoarseness was found to occur much less often and to be much less severe. They report excellent results in thirty-seven of eighty-one patients, with good results being noted in twenty-two and failures in twenty-one instances. The thicker and more copious the sputum, the better were the results with this method of therapy. They recommend the use of Tryptar inhalations before resorting to bronchoscopic aspirations in atelectasis.

TONSILLECTOMY

The relationship of tonsils and adenoids to bacterial asthma is discussed by Sobel.[127] The three major schools of thought on this subject are as follows: (1.) The tonsils and adenoids can act as foci of infection, and their removal will favorably influence the asthmatic complaints. (2.) The tonsils and adenoids play an important role in preventing the spread of infection, and their removal may precipitate asthma in an allergic individual. (3.) The indications for adenotonsillectomy are the same for allergic and non-allergic patients. Previous to allergic management, Sobel reviewed the histories of 100 asthmatic patients. Thirty-two of these did not have adenotonsillectomies, and the remaining sixty-eight had gone to surgery before coming under allergic management. Forty of these sixty-eight

patients developed asthma for the first time after their adenotonsillectomies. Twenty-eight per cent of the patients had their first occurrence of asthma within the first year after the adenotonsillectomy. In all too many instances the indications for removal of tonsils and adenoids have been predominantly for chronic nasal discharge and chronic nasal congestion. These complaints may well be part of perennial allergic rhinitis rather than indicative of infection in the nasal pharynx. It is her opinion (and this reviewer's) that too many adenotonsillectomies are performed because allergic vasomotor rhinitis is confused with recurrent colds. The severity of bronchial asthma is influenced in no measure by the presence or absence of tonsils and adenoids. This reviewer is of the opinion that the indications for tonsil and adenoid removal are the same in the allergic as in the non-allergic individual.

TYPES OF WHEEZING

Elderly patients with bronchiectasis are extremely susceptible to intercurrent infections. Pittman[102] prescribes sulfamerazine as a seasonal prophylactic therapeutic measure. She finds this most helpful and institutes the oral use of these tablets in the fall with a continuation through the winter months. She has stated that bronchiectasis in the elderly patients is usually secondary to other extensive lung changes with a resultant loss of pulmonary reserve. It is important to assist in the removal of secretions, to control intercurrent infections and to maintain a good degree of nutrition. As an alternative to the above-mentioned sulfonamid, the patient should be put upon a regimen of penicillin or aureomycin. These latter antibiotics may be given orally. Pittman believes that autogenous vaccines appear to be of some value. They should be prepared from cultures taken during an acute infection. In the management of elderly patients it must be remembered that the physician is dealing with aging tissues. This aging is not a localized condition but is a diffused process. In the bronchiecstatic patient, pulmonary fibrosis and emphysema may be present far in excess of other tissue changes.

Reversible bronchiectasis is probably a sequel to atypical pneumonia in only a small percentage of cases.[103] It is thought that reversible bronchiectasis does not occur after lobar pneumonia. The use of expectorants, drainage and antibiotics is necessary in pneumonia and post-pneumonia phases if true bronchiectasis is to be prevented. The pneumonia that appears in recurrent manner in bronchiecstatic patients is actually an episode of obstructive pneumonitis resulting from bronchial obstruction with mucous plugs. To assist in the removal of bronchial secretions, Barach, Beck and Smith[5] apply a mechanism of negative pressure to the upper respiratory passageway. This is done at the moment the peak inspiratory pressure is reached. Their apparatus includes a blower to inflate the lungs gradually to a positive pressure of 20 to 40 mm of mercury. An additional blower is used to develop a negative pressure of 20 to 40 mm of

mercury with high volume flow rates. Slow inflation of the lungs by air from the positive pressure blower is accomplished at the height of respiratory pressure. The patient then triggers a valve to the negative pressure blower permitting the expulsion of air from the lungs at a flow rate greater than the rates obtained by the greatest degree of human coughing. This portable apparatus permitted a two-fold increase in the rate of expiratory flow in twenty patients with bronchial asthma, emphysema or bronchiectasis.

The inhalation of dust from moldy hay or straw may produce a condition known as "farmer's lung." Fuller[46] believes that the complaints may be considered as a true mold infection, perhaps due to *Candida Albicans.* The complaints have been proved to be the result of irritation of the bronchial epithelium caused by the breakdown of molds spores or grass particles. The disorder may occur in three forms: acute, subacute with spontaneous recovery or chronic and irreversible. A sudden onset of dyspnea, cough and slight pyrexia has been reported in the patient of Studdert[135] following exposure to the dust of moldy hay. The complaints must be differentiated from true bronchial asthma due to a mold sensitivity. This author believes, however, that the complaints are not based upon a fungus infection of the lungs but rather upon a non-specific interstitial lung reaction to the fungus laden hay or dust. Occupational disease can result from the exposure to grain dust. In an effort to cast some light upon this problem, Cohen and Osgood[26] analyzed the case histories of nineteen workers who suffered disability. Six of their patients were considered to be atopic and five of these were skin sensitive to crude grain dust. Four of the five were also skin test sensitive to refined flours. Of the non-atopic patients two of the five yielded positive skin reactions to crude grain dust with negative reactions to flours. The authors have reviewed the necropsy reports on three of four grain workers who expired. Significant autopsy findings were emphysema and fibrosis without bronchiectasis. *Cor pulmonale* was determined in two of the three coming to the autopsy table. Though there were no pathognomonic features, the pathologic changes were competent causes for the respiratory disability which these patients had experienced. Each of the patients under study by these authors had worked in the environment of crude dust for a prolonged period of time. Their symptoms appeared in gradual fashion and were progressively disabling. Though the workers who handle crude grain may become sensitive to the crude grain dust, it is doubtful whether the sensitivity is the only causative factor in the production of this disabling condition.

Inhalation of a foreign body is usually associated with unilateral wheezing. Bilateral wheezing, as the only abnormal physical finding, has been reported with a foreign body in the bronchial tree by Black, Ravin and Furman.[9] Inhaled vegetable substance is much more irritating than metallic articles. With the suspicion of a foreign body in the air passages, fluoroscopy will show a flattened diaphragm with diminished excursion of

the lung on the affected side. An obstructive emphysema may result. The nine-year-old patient reported by these authors presented symptoms in a clinical picture simulating bronchial asthma because of persistent bilateral wheezing in perennial manner. Following the appearance of a pistachio nut after a prolonged coughing spell, the wheezing disappeared; and there was no subsequent recurrence of symptoms.

Smokers' "asthma" is characterized by a clear-cut triad of symptoms. These are chronic pharyngitis, wheezing and dyspnea and a tendency to respiratory infections with or without temperature elevation. Waldbott[148] has shown that the most characteristic and constant feature which may lead to a correct diagnosis of the syndrome is a chronic inflammation of the pharyngeal mucosa and the tonsillar area. Persistent hyperemia of the pharyngeal mucosa is noted. In this instance the paroxysms of wheezing are not nearly as distressing as those of allergic asthma. In allergic asthma, the wheezing appears throughout the lungs, whereas in smokers' "asthma," findings are localized principally in the tracheobronchial area. Vital capacity studies have shown an average decrease of only 85 per cent of normal in these patients with the triad of smokers' "asthma." Waldbott believes that habitual smokers with symptoms of bronchial asthma will find their asthmatic symptoms better controlled when smoking is completely eliminated. Editorial comment[38] suggests that the broncho-constrictor action of nicotine may account for the symptoms of constriction in the chest and the dyspnea of these patients. The condition is very common and is often mistaken for bronchial asthma or bronchiectasis. The syndrome has no allergic basis. Early cases are reversible and require only the elimination of smoking to effect a cure within about seven days.

Loss of consciousness preceded by coughing is an entity described by Kerr and Derbes.[65] The syncope is sudden and may occur while the patient is in any position. Recovery of consciousness is rapid and sequelae are minimal. The cough is dry, unproductive in character and is often a marked paroxysm accompanied by extremely vigorous muscular efforts. The definite mechanism of the syncope is unproved. Therapy consists of the eradication of the underlying cause of the cough when this is feasible. No therapy is indicated during the attack as most therapeutic measures are pointed toward prevention. Vigorous measures are indicated in those patients with serious cardiovascular disease.

NASAL AND OCULAR

Henderson and his co-workers[57] have employed cortisone for the control of marked symptoms of seasonal hay fever. Since these symptoms are characteristic of seasonal complaints of the upper respiratory tract, they prefer the title "seasonal allergic rhinitis." Satisfactory management in their cases was completed with the use of 100 mg daily in interrupted courses of a few days each period. The selected patients had shown no contraindication for cortisone use, were severely affected despite a fair

trial of conventional management and were unable to "get away" during the pollen season. They believe that the widespread use of cortisone or corticotropin must be tempered by the fact that these hormonal substances should be considered relatively heroic for such complaints as hay fever.

The unwanted step-child of ophthalmology, according to Minnes,[88] is allergy affecting the anterior segment of the globe. An accurate diagnosis of allergic lesions may be determined by a careful history, the clinical appearance of the conjunctiva and a cytologic examination of the secretion. He describes three different types of allergic conjunctivitis. The first is a sudden reaction with swelling, frequently associated with respiratory pollen symptoms. The second is characterized by a congestive reaction associated with follicles in the conjunctiva with some swelling and redness of the lids. This second classification is usually produced by cosmetics, atropine or butacaine sulphate. The third type of allergic conjunctivitis, with mucinous discharge, usually contains eosinophiles. This type of conjunctivitis is chronic, recurrent and associated with bilateral interstitial inflammation of the conjunctiva which is usually of seasonal type. The etiology for vernal conjunctivitis is stated to be unknown.

To prevent recurrence of nasal polyps it is necessary to correct or eliminate the etiologic factors. Part of the preventive program also includes radical extirpation of the growth and effective post-operative measures. Hollender[59] believes that nasal polyposis may be a collagen disease. They can be cured only by surgical removal with palliative remedies (cortisone and ACTH) being considered without value. Radium irradiation is begun about two weeks after the operation as this is further assurance against re-growth. It is often necessary to give two or three treatments at intervals of about three weeks. This author considers allergy as an important factor in polyp formation.

Injection of cortisone into the interior turbinates of patients with coryza has been done and reported by Wall and Shure.[149] On the average, four doses of 2.5 to 5 mg suspensions of cortisone produced improvement of rather prolonged duration. The dose of cortisone at each injection was 0.1 to 0.2 cc. Patients with vasomotor rhinitis were less responsive to this form of therapy.

The most common causes for chronic congestion of the nasal passages are excessive blowing and use of nasal vaso-constrictors. Hunnicutt[61] advises his patients not to blow their noses nor to use nasal medication. He prefers oral preparations for the relief of nasal congestion.

Baxter and Rose[6] found the degree of the allergic reaction in nasal mucosae of patients with nasal allergy to be quite variable. This was true with or without the presence of mucous polyps. They have found that a ratio of 3-5 to 1 remains quite valid for both anteromucous membrane and nasal mucous polyps when dry weight is compared to wet weight. Upon this finding, they feel that a dilution factor does not play a major role in any variation of histamine which may occur in nasal mucous polyps

with varying degrees of allergic symptoms. Their complete figures reveal no significant difference by wet weight of tissue in the histamine content of nasal mucous polyps when compared as such with that of normal mucous membrane. With increasing degrees of nasal signs and symptoms there is a decrease in the histamine content of the nasal polyps. In other words, an increase in the severity of the allergic reaction is associated with a decrease in the histamine content of the nasal polyps. They have summarized that there is no correlation between the degree of nasal allergy and the blood, nasal smear and tissue eosinophilia. Likewise, there is no correlation between the degree of tissue eosinophilia and the histamine content of nasal mucous polyps.

As a result of the publicity given to a particular California region as "mecca" for asthmatic patients, several California allergists were questioned regarding their experience in this connection.[106] It was the consensus that the published article caused considerable disturbance in the minds of both patients and physicians. Few of the answering physicians were of the opinion that there was anything definite in this area which could be of benefit to the average asthmatic patient. None of the physicians recommended that patients come to that particular area of California unless they were advised to do so by their own physician and could afford to stay in that area for a sufficient length of time to determine whether or not the climatic change would be beneficial. Inasmuch as climate is only one factor in the etiology of asthma, it is seldom the experience of most of us to find that our patients will show marked improvement with this change in climate.

Another question[107] circulated by the Society concerned the concomitant development of hay fever and asthma symptoms with an episode of serum disease. Few of the physicians had seen instances where they thought serum sickness precipitated allergic complaints. Personally, this reviewer has not had the experience of having a patient develop symptoms of seasonal hay fever and asthma as a result of previous serum disease. The initial onset of respiratory allergy may be hastened by a reaction of serum sickness character. The most frequent complication of serum sickness in my experience has been prolonged urticaria or dermatographia. I am sure we have all seen those patients who find themselves clinically sensitive to foods or inhalants only during the pollen season, with apparent immunity to the same materials in the non-pollen periods.

HEADACHES—MECHANISM

The most frequent complaint of patients reporting to their physicians is headache. The arterial structures are the most frequent source of headache, particularly when these are dilated and distended. Tunis and Wolff[144] list the six basic mechanisms of headache from intracranial sources. These are: (.1) traction on the venous tributaries to the venous sinuses from the surface of the brain, (2.) traction on the middle

meningeal arteries, (3.) traction on the large arteries at the base of the brain, (4.) distention and dilatation of intracranial arteries, (5.) inflammation in or about any of the pain sensitive structures of the head and (6.) direct pressures by tumors on the cranial and cervical nerves. Vascular headaches, as characterized by the migraine syndrome, are most frequently observed with dilatation and distention of one or more branches of the superficial temporal artery. To establish a clinical diagnosis of vascular headache, the physician must consider the following important points. This type of headache is periodic and associated with nausea, vomiting or anorexia. Transient visual disorders may just precede the headache. There may be a family history of vascular headaches. The pain is usually unilateral in the earlier stages and is associated with unilateral lacrimation, a suffused conjunctiva and partial nasal obstruction and facial flushing on the side of the head pain. Ergotamine tartrate is the best agent to restore the dilated vessels to a non-painful constricted state. If the parenteral use of ergotamine tartrate fails to relieve the headache within an hour, other drugs should be employed to raise the pain threshold. They regard ACTH as a research implement and not as an adjunct in the practical management of migraine headache. Wolff and his co-workers[157] believe that vascular headaches are precipitated by marked vaso-constriction succeeded by dilatation. Intramural vascular edema and lowered pain threshold are associated complaints and findings. Marked dilatation and tortuosity of the conjunctival arterioles, capillaries and venules on the side of the headache are also noted. There is a more or less continuous alteration in the contractual state of the cranial vessels in these patients subject to vascular headaches.

Smith[126] believes that allergy is extremely important in headache inasmuch as these complaints occur twice as often in allergic individuals or in association with other allergic findings. He has employed the intravenous use of dihydroergotamine in 1 cc dosage for the relief of histaminic cephalalgia. This reviewer has used this medication on one occasion with dramatic results after other measures had failed. At the 1953 meeting of The Southwest Forum of Allergy the question was raised as to what measure of relief could be extended to the patient during his attack of histaminic cephalalgia. Most of the attendants were in agreement that the best immediate relief could be obtained with epinephrine 1-1000 even though such relief was of short duration. It may be wise to add intravenous dihydroergotamine (DHE 45) to the preparations suggested for the relief of this acute attack. Relief is present in one to five minutes following intravenous administration if such relief is going to be obtained. The author employed the same preparation by vein for the relief of tension headache. He considers true migraine as a symptom complex and not as a disease entity. Twenty-five per cent of patients with migraine headache are helped in some way by allergic management.

Several factors must be considered as a background for headaches.

Ogden[94] believes that frontal headache is essentially due to a reflex mechanism in which dilatation of certain vessels results from nasal mucosal edema. It must be remembered that several factors may be responsible for the patient's complaints. Because of this, he uses an effective vaso-constrictor with an analgesic combination. If the stress factor is high, there may be need for suitable sedation. Suitable allergic management including hyposensitization, antihistamines and other measures are necessary where the allergic factor is considered to be of marked importance. He holds tension as only one factor of many as causative of headache. The term "tension headache" is too all-embracing to be definitive.

HEADACHE THERAPY

Ischemia of the brain may be improved by histamine therapy according to Furmanski.[47] The administration is completed in the usual manner familiar to most men practicing medicine today. The dilution is that of 5.5 mg of the histamine phosphate in 1000 cc of 5 per cent dextrose in saline. The intravenous injection is begun at a rate of 20 drops and gradually increased to the flush level. Benefits should appear within a two-weeks trial or the method of therapy is discontinued.

Thirty-five patients with Ménière's disease were treated with intravenous procaine by Fowler.[42] These patients had failed to respond to oral nicotinic acid—benedryl—hyoscine therapy. It was theorized that the procaine-nicotinic acid given by intravenous route would relieve the spasm of labyrinth vessels and increase the blood flow to those areas. The author believes that this method of therapy was not a panacea for Ménière's disease but employed it as a valuable tool in some resistant patients. Various causes for Ménière's disease have been listed by Laub.[76] These include vaso-constriction, vaso-dilatation, allergy, histamine sensitivity, autonomic dystonia of the labyrinth and others. He reports two cases of Ménière's disease that are felt to be upon an allergic basis. One of these had a dramatic improvement with the use of an antihistaminic agent. Lewy[78] has found dramamine and histamine to be poor preparations in the treatment of Ménière's disease. He prefers nicotinic acid, antihistamines and allergic management as the results are much more satisfactory. The most effective results in Ménière's disease are obtained with therapeutic measures directed at the pathologic physiology.

Vaso-constrictor drugs have been employed in an attempt to prevent and treat migraine headaches. Blumenthal and Fuchs[12] obtained best results with the subcutaneous or intramuscular injection of Octin (methyl-iso-octenylamine). Best relief was obtained with the administration of this preparation at the onset of vaso-dilating type of headache. Rectal and oral routes of administration were not accompanied with the success of the above method. This reviewer can recall one patient with typical histaminic cephalalgia who employed octin by mouth. Though he did not obtain complete relief from his periodic attacks, the severity and duration

of his symptoms were definitely decreased. The preparation had no influence upon the recurrence of subsequent headaches as determined by the ingestion of octin over a rather prolonged period of time. These same authors[13] use the term "tension headache" when physical or nervous tension produces or aggravates a headache regardless of the primary cause. Anxiety, overwork and fatigue may be the sole causes of symptoms or they may act as added strains where other etiologic factors are present. Gentle sedation and analgesia are of benefit. This can best be obtained with Fiorinal (Sandoz), in their opinion. In some instances the excessive intake of caffeine, as in coffee, appears to play a role in relieving headaches through its vaso-constrictor action. Lanzarot[73] has shown that the electrocardiographic changes brought about by ergotamine cannot be ascribed to a peripheral interruption of the neurohumoral sympathetic impulses. Low T wave potential and marked decrease of the total potential in the precordial leads were the most consistent changes noted during attacks of migraine. The electrocardiograms were normal before and after attacks. All electrocardiographic changes were reversible with intramuscular injection of .25 mg of ergotamine tartrate. This was thought to be due to the vaso-constricting and sympathicolytic actions of the ergotamine tartrate. When drugs which were vaso-dilators and possessing sympathicolytic properties as well were employed, the reversibility of the electrocardiographic changes was noted.

Migraine patients and those with histamine headaches were well relieved with suppositories containing ergotamine tartrate and caffeine. Magee, Westerberg and Dejong[83] found that patients with tension or psychogenic headaches were not relieved by this preparation. They were impressed with the synergistic action of caffeine and ergotamine. Excellent results were obtained in thirty-five of fifty-seven patients with migraine. Side effects of this medication consisted of nausea, vomiting, cramps in the abdomen and legs, light-headedness, numbness of the extremities, palpitation, sweating and sleepiness. Of these, the only frequent and significant side effect was considered to be nausea. The presence of side effects was thought to be due to the dosage employed. It was eventually found that one-half of the initial suppository dosage was quite beneficial without any unpleasant reactions. Superior relief was obtained with the suppository form of medication than when the similar compound was given by oral route. Ergotamine tartrate was employed by Clawson[23] in the relief of migraine headache. He states that the preparation acts by causing prolonged vaso-constriction and interrupts the pain-producing mechanism by direct stimulation of smooth muscle. The dosage employed orally was that of two tablets of Cafergot at the onset of the headache and one tablet every hour until six tablets had been used.

Peters[100] considers migraine to be a psychosomatic disorder with a definite hereditary tendency. Between the extremes of typical migraine and typical tension headaches there are all degrees or combinations of migraine-

tension headaches. The migraine headache will respond to ergotamine products while the tension headache will not. Cafergot, when tolerated, will usually control mild to moderate headaches but will not affect the severe headaches in most migrainous individuals. Rectal suppositories of this preparation have several advantages. Among these is that the suppositories may be used by the patients early in the attack. They can also be used in the presence of nausea and vomiting. For individuals who are unable to take ergotamine preparations—those having peripheral vascular disease, advanced hypertension, coronary disease, angina pectoris, impaired hepatic or renal function or pregnancy—many find relief with the use of methyl-iso-octenylamine (Octin). Best results are obtained with this latter preparation by intramuscular route in a dosage of 0.5 cc to 1 cc.

DERMATOLOGY

The irritating effects of soaps and detergents may be related to the extent to which they denature skin proteins. It is highly probable that alteration of keratin is an important mechanism in the production of dermatitis. Van Scot and Lyon[147] have tested various commercial preparations for their sulfhydryl-exposing capacity on human keratin. The effect upon plantar keratin was most noticeable in the detergents rather than in the usual soaps. Those preparations producing a greater alteration of keratin are not more likely to cause dermatitis of the contact type, however. Soaps are irritating to the skin in some individuals and under certain conditions. They may also initiate, aggravate or prolong skin injury.

Nelson and Stoesser[92] state that the quality of soap manufactured is governed primarily by the nature of the fat or fats contained. Most of the commonly used toilet soap bars are not pure soaps. Substances such as rosin impart softness and produce a more soluble and faster sudsing soap, particularly in cool water. Soaps employed for dishwashing, laundry and household cleansing contain alkaline "builders" to increase their cleansing qualities. These builders may be sodium carbonate, trisodium phosphate and pyrophosphates. Much of the irritation caused by soap has been ascribed to its alkalinity. This produces swelling of the horny layers of the epithelium as well as a partial debridement of this layer. In those patients with a true soap dermatitis the only solution is the substitution of non-irritating cleansers for both toilet and general household use. Synthetic detergents are surface-active organic compounds containing both hydrophilic and hydrophobic groups. Liquid detergents have also been used though they are not as convenient or economical as bar or cake forms. In their patients with eczema they have found that Lowilla cake is relatively hypoallergenic and therefore is the most valuable in the therapy of this skin complaint. This preparation is also an ideal cleanser for the skin of the newborn infant.

A practical and interesting discussion of the treatment of common skin disorders has been presented by Burman.[19] Usually the treatment of

cutaneous disease is planned for symptomatic relief. Since a single symptom may have a very complex background, the above approach is a fallacious one. Burman warns against over-treatment because rapid changes of preparations may be irritating alone or in combination. Therapeutic dermatitis has become a definite problem. He recommends the use of compresses with Burow's solution diluted 1 to 16 or 1 to 20. Potassium permanganate or boric acid solutions are also recommended. It must be remembered, however, that the danger of absorption of boric acid is a matter of much concern at the present moment. In agreement with Nelson and Stoesser, this author also believes that soap should be avoided for cleansing purposes. Substitutes such as Lowilla cake, Phisoderm or Dermolate should be used cautiously. Colloid baths, however, are the most safe and satisfactory method for cleansing the skin. Drug sensitivity is given some consideration. Sensitivity to drugs is remarkably specific. The types of eruption which may be produced by drugs are various and all-inclusive. When the skin is involved as an expression of drug sensitivity, the withdrawal of the offending drug is usually effective in curing these eruptions. However, bromide and iodide skin eruptions will require auxiliary methods of treatment. The proper care of any patient with dermatologic symptoms requires a proper evaluation of that individual from all local and systemic standpoints.

The absolute and relative indications for the use of ACTH and cortisone have been listed by O'Leary and Erickson[96] as follows: (1.) Any self-limited hypersensitivity reaction of severe degree unresponsive to more conservative measures. These include acute urticaria, drug eruptions, acute angio-edema, contact dermatitis of severe degree and erythema multiforme. (2.) Serious or otherwise fatal conditions such as pemphigus and systemic lupus erythematosis. These preparations are not used in neuro-dermatitis, psoriasis and seborrheic dermatitis because of the short duration of the improvement and the frequency of severe relapses after the original course of therapy. The majority of skin diseases are not indications for the use of these hormones. They caution very strongly against the unnecessary and overenthusiastic use of cortisone and ACTH in the treatment of the usual skin disease.

A study of fifty-two private patients with refractory acne has been reported by Pensky and Goldberg.[99] The fractionated liver extract employed by these authors has been prepared from liver injections of crude USP material. Vitamin B_{12} is lost. The preparation is also free of the hypertensive and hypotensive fractions of liver extract. Their fifty-two patients were comprised of thirty-five females and seventeen males. Severe acne with pustules, cysts, seborrhea and scars were present in most of these patients. Each patient received an average of 2 cc of the fractionated liver extract twice weekly. Treatment was continued from twelve weeks to one and one half years. Good improvement was noted in thirteen instances with moderate benefit being experienced by twenty patients. Other

measures were used for the treatment of the acne with the authors, therefore, considering the liver extract, as employed, to be a useful adjunctive method of extending the therapeutic potential in acne.

Four categories of skin diseases related to light sensitivity are discussed by Kesten and Slatkin.[66] The first category includes solar erythema, urticaria and photodynamic dermatitis. Porphyria, hydroa vacciniforme and epidermolysis bullosa make up the second category. The third classification includes pellagra, lupus erythematosis, papular urticaria and others. Chronic sun burn, epithelioma and degenerative diseases of collagen and elastic tissue are included in the fourth category. These authors describe the means by which these patients may be protected.

Four patients are cited by Reyer[111] with exacerbation of their rhus dermatitis by antigen injections. These four patients were not allergic in their personal or family histories. Each injection of rhus antigen seemed to produce a gradual and steady progression in the severity of the dermatitis. He believes that each patient has his own level of tolerance for any antigen. Therefore we should assume that one standard dosage of rhus antigen will not benefit all lesions. Most proponents of the antigen form of therapy for poison ivy dermatitis have lost sight of the fact that the skin lesions are upon a basis of true contact and have never been proved to be on an accepted antigen-antibody foundation.

Widespread cutaneous involvement may be seen with trichophytin rubrum infection. Lewis, Hopper and Scott[77] report three cases of this condition with co-existent lymphoblastoma. The authors have presented no evidence showing that the fungus was capable of causing lymphatic disease, and the possibility of chance association between these two was considered remote. They advised that all widespread and atypical manifestations of fungus infection be studied mycologically. Swinny[136] thought the greatest difficulty in making an accurate diagnosis of tricophyton rubrum infection is the inability to obtain a good culture growth. In the study of skin test reactions using tricophyton and monilia extracts, a report was made to Swinny of one instance in which a positive culture for tricophyton rubrum had been encountered. In subsequent correspondence, Swinny informed this reviewer of his difficulties in obtaining a good culture of this particular fungus. He postulated then that it might be a difference in the various strains.

Tachau[138] believes that a differentiation must be made between infantile eczema, seborrhea and intertriginous dermatitis. Atopic dermatitis has been described as a diffuse, inflammatory infiltration associated with intense itching. Lichenification is the exception in infancy. Secondary eczematization is evidenced by the appearance of vesicular lesions. This author places no reliance upon skin tests for the determination of true etiologic factors. This is in complete agreement with the thoughts held by this reviewer. Any therapeutic measure employed in the treatment of infantile eczema should be correct local treatment. Crude coal tar is per-

haps the most valuable application that can be employed, but it must be used with good care. Antibiotic and antihistaminic agents are of limited, if any, use in the treatment of infantile eczema. Excellent results, according to the author, are obtained with radiotherapy. A safe, efficient dose of 30 r can be used in the face of failure with other methods of therapy. Important features include the correction of environmental allergy or any maladjustments of general health.

The question has been raised as to whether a small child with eczema should be vaccinated against smallpox. It has been suggested[104] that it is not necessary to withhold smallpox vaccination from a child with localized atopic eczema. It is suggested, however, that it might be desirable to vaccinate such a child at a time when the eczema is quiescent rather than during a flare-up. In the opinion of this reviewer, any child with atopic eczema should not receive smallpox vaccination during the time that lesions of any consequence are in evidence. The lesions should first be cleared with proper management. Then, during an interval of freedom from skin lesions, vaccination for smallpox can be completed.

Gaul[49] reports a low incidence of metal sensitivity in sixty-eight cases of hand eczema. Incidence of sensitivity to chrome metal was found to be 3 per cent of the total patients studied. A predisposing factor to metal contact dermatitis is thought to be the wetness of the skin from perspiration. Most of these patients have more trouble in the summer seasons than they do during cool weather. The total incidence of sensitization to various metals in his patients was 11 per cent. Most of the sensitive patients demonstrated definite reactions for nickel. There was a ten to one sex ratio of metal sensitivity with the higher percentage being noted in females. The author suggests that perhaps the jewelry customs of women might be the explanation for this differentiation.

Cholinergic urticaria is a term used for hypersensitivity to heat in which attacks may be reproduced by administration of acetylcholine derivatives. Kerland[67] discusses the patients in which hypersensitivity to cold and heat may show some influence upon their reactions with exertion or emotional stress. The manifestations of this condition may be either local or systemic. Systemic reactions may be quite severe with syncope and unconsciousness being noted.

ALLERGIC PURPURA

A diagnosis of cryoglobulinemia was made by Steinhardt and Fisher.[131] The suspicion of this condition was aroused by the presence of a gel-like appearance of the blood, high sedimentation rate in the absence of infection or neoplasm and associated urticaria caused by cold with purpura. They could determine no appreciable difference in the onset, size and duration of the wheal reaction to cold exposure after the administration of ACTH and cortisone. The associated findings of purpura were improved following the use of these hormones. The degree of cryoglobuline-

mia was influenced by hormone therapy in that the precipitable portion of the serum was reduced from 12 to 18 per cent of the total serum volume to approximately 4 per cent. Passive transfer studies were unsuccessful in this instance of cold urticaria. Reverse passive transfer studies in cold urticaria were not demonstrated. Benadryl by intravenous route did cause a reduction in the size and duration of the urticaria following exposure to cold. The authors postulate that cold urticaria in their patient may have been related to local histamine release.

Hypoplastic type of aplastic anemia with thrombocytopenia and purpura has been reported by Thompson and Rowe.[148] This fatality followed the intermittent use of chloramphenicol over a two-year period. Their interesting case report presented predominant symptomatology due to hemorrhage in the subcutaneous tissues, nasal mucosa, urinary system and the brain. Therapeutic measures included whole blood transfusions, hormonal agents, liver extract and symptomatic measures. The chloramphenicol had been taken over a two year period in intermittent fashion. This should serve as a good warning that this drug is capable of producing marked and irreversible changes in the hematopoietic system of a sensitive individual.

Thrombocytopenic purpura as a result of hypersensitivity to quinidine is reported by Larson.[75] The causative agent was confirmed by the administration of 0.2 grams of quinidine sulfate by mouth under basal conditions. The author felt that there was a specific peripheral action by the quinidine on the circulating platelets. So rapid was the decrease in platelet count that the rapidity could not be explained upon inhibition of bone marrow formation. Following the addition of small amounts of quinidine to the patient's whole blood, clot retraction could be inhibited. Larson felt that this was a definite antigen-antibody type of reaction. The purpura did not recur after the quinidine had been discontinued.

Ackroyd[2] divides allergic purpura into: (1.) that which is associated with erythema with joint and visceral symptoms and (2.) true purpura which is never associated with an erythematous exanthem. The first type (Henock-Schonlein type) is seldom due to food sensitivity. This might be considered to be the idiopathic type of purpura. Though there is no real proof, this form of purpura may be a manifestation of bacterial allergy. True purpura, which is never associated with an erythematous exanthem, occurs in the absence of inflammation. Food allergy here plays a rare role, but the purpura may occur at the height of an infection or during convalescence from an infectious disease. Thrombocytopenia, upon a drug sensitivity basis, is due to an antibody production of platelet lysis. In infection the purpura is due mainly to the action of the infectious process upon the megakaryocytes. Regardless of the type of etiology, however, capillary fragility is increased, resulting in subcutaneous or mucous membrane hemorrhage. Piraino[101] has reported an instance of Schonlein-Henock syndrome in which penicillin was suspected to be the chief causa-

tive factor. Egg sensitivity in his patients was considered as a secondary agent. The joint symptoms of this condition resemble serum disease. This form of purpura can be readily differentiated from other types because of a normal prothrombin time, bleeding time, clot retraction time, blood platelets and coagulation time. Though death can occur, the prognosis is generally good. Nephritis is the most frequent and serious complication.

GASTROINTESTINAL PREDISPOSITION

The question has been raised as to whether any vitamin or mineral imbalance could predispose to a food sensitivity.[105] One consultant felt that the tendency for allergic reactions to develop is not mediated by excesses or deficiencies of either vitamins or minerals. If the diagnosis of food allergy in the question brought to his attention were accurate, this one consultant suggested the oral desensitization for food sensitivity. The second consultant felt that relief obtained with the elimination of specific foods and the return of symptoms with their re-ingestion indicated food allergy as the probable diagnosis. It was his impression that some patients were allergic to almost all foods as other patients may be allergic to almost all pollens. In the opinion of this reviewer, this latter statement is going "overboard" on the subject of food allergy to a good extent. Emphasis in food allergy and the recording of food sensitivity should not be made upon skin test negative or skin test positive foods. Trial diets and food diaries are much more reliable.

Kaufman[63] has described the clinical features of disorders in which the ingestion of allergenic foods produces a variety of musculoskeletal syndromes in susceptible individuals. The signs and symptoms may be confined to muscles or joints or they may involve both of these locations. Allergic rheumatism and allergic arthritis are included in this category with musculotendinous structures being involved in the former classification, and the articular tissues affected in the latter. The latent period between ingestion of a threshold dose of the offending food and the first appearance of signs and symptoms may vary from a few minutes to several hours. Allergic reactions in the musculoskeletal system may be intermittent and short-lived; they may last for several days; or in some individuals, be present without exacerbations or remissions. The most satisfactory treatment for this condition has been the elimination of the offending food from the patient's diet. A form of rotary dietary management has been suggested to minimize the likelihood of recurrences.

Seventy per cent of the histamine which reaches the liver by way of the portal vein is inactivated by that organ in guinea pigs. These were the findings of Naranjo and Naranjo.[90] Their investigative procedures were based upon the knowledge that antihistaminic drugs are less effective when given by mouth than when given parenterally. The question is raised, therefore, whether this difference depended upon absorption from the gastrointestinal tract or upon the fact that the antihistaminic drugs are

inactivated in the liver in the same manner as histamine. The seven antihistaminics studied by these authors were: Neo-Antergan, Multergan, Hista-3, Phenergan, Neohetramine, Trimeton and Thephorin. All of these were inactivated for the most part by the liver. Hepatic inactivation varies from 70 to 90 per cent. Thephorin was least activated at this source (39 per cent). Neo-Antergan and Multergan were the antihistaminic drugs with the highest hepatic inactivation (90 per cent). Based upon their studies, they concluded that the antihistaminics, like histamine, are inactivated in the liver and not in the gastrointestinal tract. This may explain in some part why antihistaminic drugs are of greater value when given parenterally, to be absorbed by the portal vein, rather than when given by mouth.

SYMPTOM PICTURES

The manufacture of corn starch is completed in such a way that most of the soluble proteins, minerals and oil-containing germ centers of the original whole corn are removed or cleaned away. Since corn starch is practically free of protein, allergic reactions to its ingestion have been rare. Spielman[130] has reported one patient allergic to corn starch and other corn products except corn sugar. Blindfold ingestion tests were given to his patient on five separate occasions with tapioca causing no reaction. Definite immediate symptoms were experienced from the ingestion of corn starch, regardless of the material used to sweeten the preparation. Corn oil produced no reaction in this corn-sensitive patient.

Foods and pollens as the major causes of chronic ulcerative colitis is the basis of a report by Rowe, Rowe and Uyeyama.[120] In their first patient the diagnosis was made by history of x-ray findings. Milk sensitivity was determined to be the cause of abdominal pain, cramping and diarrhea. Relief was experienced upon a milk free routine with symptoms being reproduced by the ingestion of milk. Obstruction of the terminal ilium, necessitating resection of a part of the bowel was found to be caused by sensitivity to milk, eggs and fruit in another patient. Until these allergenic foods were completely eliminated from the diet, the patient continued to have definite symptoms of enteritis. An allergic basis for regional enteritis is, in the opinion of these authors, a necessity based upon the remissions and exacerbations, elevated temperature, localization of complaints and the relief of symptoms obtained with x-ray therapy and cortisone.

Food sensitivity may have a definite influence upon nutrition, growth and the mental attitude of the patient. Reicher[112] reports a patient seventeen years of age but in appearance no more than twelve or thirteen years. This individual was thin, sickly, pale undernourished and underdeveloped with an ichthyotic skin. Bronchial asthmatic complaints had been a source of distress and discomfort since early childhood. Symptomatic therapy and elimination measures were attempted over a period of several weeks. No change for the better could be determined on this management. Upon

further questioning it was determined that the ingestion of American cheese was followed by asthmatic complaints. His symptoms could be reproduced with the ingestion of this food and relieved with its elimination. Reicher considers this to be the only positive proof of a specific allergen in the dietary line.

It is particularly distressing when an individual sensitivity for a food or a group of foods is a problem of interference in his profession or calling. Brown[17] describes a Catholic priest with a diagnosis of hay fever, bronchial asthma and severe distressing urticaria. The urticaria was of sufficient severity to be disabling. The lesions affected not only the skin with typical wheals and generalized pruritus; but also the mucous membranes of the mouth, throat and glottis were involved. By investigative measures, Brown was able to determine that grape wine fell under strong suspicion. This was based upon the knowledge that while on a very restricted diet the patient was permitted to say Mass each morning. In spite of the strict dietary measures, there was no amelioration of symptoms. The pattern was changed in that the urticaria and pruritus came on about ten minutes after Mass was started. Upon being skin tested for grape and raisin, large positive reactions were obtained to intradermal and pressure puncture tests. A violent constitutional reaction was produced with the ingestion of 2 ounces of wine at a later date. Grain alcohol produced no untoward effect when ingested in the same concentration as wine. When grape and grape wine were not ingested there was a complete clearance of all symptoms. Attempted oral desensitization was without success. Here is a patient whose vocation makes it impossible for him to take part in a religious community unless he says Mass. The ingestion of grape in any form will cause marked symptoms of cough, bronchospasm, urticaria and pruritus.

In the opinion of many allergists, skin testing with food extracts is of little or no value. This impression has been given a good foundation by the studies of Bloom, Markow and Redner.[11] They utilized the following foods in their study: cocoa, orange, beef, milk, wheat, egg, chicken, corn, potato and string bean. Digests of each of these foods were prepared using pepsin and trypsin as additives. Subsequently thirty patients were used, and the ten foods under study were given. Each patient was tested with the usual food extract, the pepsin digest and the trypsin digest in equal concentration. Feeding tests were also done with these foods. Of 125 negative tests with standard extracts, fifty-six were negative on tests with both the pepsin and trypsin digests, twenty-six were positive on test with pepsin digest, twenty-nine positive on test with the trypsin digest and fourteen were positive with both pepsin and trypsin digests. One hundred and ninety-five positive reactions to skin tests with standard extracts were determined. Seventy-five of these were positive to the standard extract alone, thirty-four were positive to the pepsin digest, forty-

one to the trypsin digest and forty-five to both of the prepared digests. Sixteen patients reported positive clinical trials with 268 intentional feeding tests using the ten foods under study. The opinion has been expressed in the past that certain delayed clinical reactions to foods are due to the effects of digestion upon food. The patient is not sensitive to the unaltered protein of the food eaten but to the product of this digestion. These investigators were concerned primarily with sensitivity to digests of foods by means of the skin test and to confirm such sensitivity with intentional feedings. Cases with specific sensitization to the products of food digestion appear to be limited in number. These authors conclude that it is quite infrequent that the antigenicity of foods is altered as a result of digestion. They conclude that foods play a minor role when compared to the importance of inhalant factors and infection.

The importance of gastrointestinal food allergy as a cause of infantile diarrhea has been re-emphasized by Kunstadter and Schultz.[70] In the eleven allergic infants studied, 23.5 per cent developed their symptoms within the first three months of life. A typical history in all cases revealed many changes in cows' milk formula and often goats' milk. Laboratory studies contributed no positive evidence for idiopathic celiac disease, fibrocystic disease of the pancreas or enteric infection. The diagnosis of celiac syndrome is based upon an awareness of an allergic etiology. The response to the complete elimination of cows' milk and all dairy products from the diet is of utmost importance as a diagnostic procedure. After the usual patient with celiac syndrome recovers from the diarrhea, other forms of allergy such as hay fever, asthma, eczema and allergic rhinitis develop. This is true in many instances. The authors believe that skin testing is not a dependable method for the determination of food allergy.

Allergic parotitis as a clinical entity has been described by Swinny.[137] His patient, a woman aged thirty-one, had a chief complaint of recurrent swelling of the parotid glands. Some attacks were unilateral, other attacks being bilateral. The symptoms had been present intermittently over a period of nine years. He was able to obtain a clear, thick, jelly-like cast from one parotid duct with this material containing 100 per cent eosinophiles. An elimination routine for environment and diet produced good improvement. After the disappearance of the parotid swelling on a skin negative diet, positive foods were returned to her regimen. All were without clinical significance except wheat, which was followed in two hours with an attack of parotid swelling and in twenty-four hours by anal itching. A wheat free diet maintained the patient without complaints. Swinny's pattern of allergic parotitis includes a personal or family background of allergy, recurrent attacks of unilateral or bilateral swelling of the parotid glands, thick ropy sputum with many eosinophiles with the attacks being precipitated by specific allergens inhaled or ingested. Relief and prevention is maintained by avoidance or hyponsensitization.

ALLERGY TO INFECTION

Brucella sensitivity is classified as the tuberculin-type. In association with clinical, biological, radiological and therapeutic aspects this test is an aid in the diagnosis of patients, particularly those with negative blood cultures. Martorelli[84] has found in some instances the only clinical manifestation of allergy attributable to brucellosis to be pruritus. He feels there is a need for a strict standardized intradermal test which will give evidence of brucellar hypersensitivity.

The antibodies of bacterial antigens do not appear to attach themselves to epithelial tissues. They produce or aggravate the general symptoms ordinarily associated with the rheumatic diseases, characterized by pain, swelling and stiffness. Small and Small[125] imply that these bacterial antigens seek out antibodies attached to the cell of white fibrous tissue. They noted cumulative effects resulting eventually in overdosage when their treatment dosages were spaced at fourteen days or less. On the other hand, perennial therapy at intervals of twenty-eight days had not shown this feature. They were able to repeat bacterial antigen administration month after month with consistently good results. The small doses in the early days of therapy do not ordinarily give a period of improvement of fourteen days' duration; but whatever the length of the improvement, a second dose should be administered as soon as possible after the relapse which terminates it. Symptoms of overdosage frequently follow the second injection. They have largely eliminated these symptoms of overdosage since they regard the relapse at 50 per cent utilization of the preceding dose. Their treatment schedule works toward the perennial plan of treatment with administration of the antigen at intervals of every three to four weeks.

Stevens[133] has found respiratory reactions to follow inoculation with vaccine. These reactions have occurred most frequently at some level of dosage during the therapeutic injection of bacterial filtrates. Because of the time when therapy is instituted, most reactions occur in the middle or late winter when the doses are large. It is during this season when infections have been prevalent that it is difficult to distinguish between a reaction and a mild infection. He has observed the sensitization of nasal mucous membranes to filtrates on thirty children during the past few years. Nine of this series have been completed. The upper respiratory mucous membranes of these children were hypersensitive to bacterial products in polyvalent filtrates. This same author[134] reports that asthma may occur with colds in children if they are focally hypersensitive to the bacteria causing the second stage of the cold. The patients under study were under seven years of age, and each reacted to several of the most commonly reacting allergens. None of them had asthma between colds and during the summer; so it was believed that they were not clinically sensitive to the reacting materials. In patients with asthma caused by several allergens, there is always a possibility that the virus or the bacteria

complicating a cold may be the cause of a clinical attack. In these instances, the respiratory membranes need not be specifically sensitized to bacteria. Sudden changes in temperature and humidity, mechanical irritation, exercise or excitement may act as non-specific aggravating factors in allergic asthma. In the strictly infectious type of asthma the attacks occur only in association with definitely proven, infectious head and chest colds during the winter season with complete freedom from complaints during the summer. These patients require bacterial therapy. All too often the mothers of patients will state that their children have asthma only in association with a head or chest cold. Unless the allergist is well aware of this means of description he will overlook the fact that many "summer colds" are in reality symptoms of misunderstood seasonal hay fever.

Fries and Borne[45] point out that upper respiratory and other bacterial infections may have an adverse effect on the course of chronic allergic symptomatology. They observed thirty-two allergic children showing temporary remissions of their allergic symptoms following a viral or bacterial infection. The so-called "anergic" phase became apparent at the height of the febrile period and continued for from five days to one year. These authors note that there is no constancy of beneficial effect of bacterial infection or of induced fever on the allergic state. Almost without exception the allergic symptoms recur. They theorize that the relief of allergic symptoms with temperature elevation may be produced by some hormonal influence. Coincidence must be removed from consideration when the many instances of sudden interruption of asthma or perennial rhinitis or severe, chronic, eczematous rash have been noted. The provocative factor in producing these remissions of the allergic state would tend to be the fever which accompanies the infection in these patients. They suggest that the treatment of allergic diseases may rest in this phenomenon of interference.

REFERENCES

1. Abramson, H. A.: Psychosomatic allergy and its management (special article). Quart. Review of Allergy and Appl. Immun., 7:197 (June) 1953.
2. Ackroyd, J. F.: Allergic purpura, including purpura due to foods, drugs and infections. Amer. Jour. Med., 14:605, 1953.
3. Allen, G. W.: Black widow spider (Latrodectus mactens) poisoning treated with D-tubocurrarine chloride. Ann. Int. Med., 39:624 (Sept.) 1953.
4. Angerer, A. L.; Su, H. H.; and Head, J. R.: Death following the use of Efocaine. JAMA, 153:550 (Oct.) 1953.
5. Barach, A. L.; Beck, G. J.; and Smith, W.: Mechanical production of expiratory flow rates surpassing the capacity of human coughing. Amer. Jour. Med. Sc., 226:241, 1953.
6. Baxter, J. D., and Rose, B.: The histamine content of allergic and non-allergic human nasal mucous membrane with simultaneous observations of the eosinophils. J. Allergy, 24:18 (Jan.) 1953.
7. Beck, C. A.: Subacute bacterial endocarditis in penicillin sensitive patients. JAMA, 153:1170 (Nov.) 1953.
8. Berkowitz, M.; Glaser, J.; and Johnstone, D. E.: The incidence of allergy to drugs in pediatric practice. Ann. Allergy, 11:561 (Sept.-Oct.) 1953.
9. Black, I.; Ravin, N.; and Furman, M.: A foreign body in the respiratory tract with symptoms simulating bronchial asthma. Ann. Allergy, 11:46 (Jan.-Feb.) 1953.

10. Blanton, W. B., and Blanton, F. M.: Unusual penicillin hypersensitivities. J. Allergy, 24:405 (Sept.) 1953.
11. Bloom, S.; Markow, H.; and Redner, B.: Studies in food sensitivity. II. The effect of protein digestion on antigenicity of foods as determined by skin tests and clinical food trials. J. Allergy, 24:64 (Jan.) 1953.
12. Blumenthal, L. S., and Fuchs, M.: Headache clinics IV. The use of Octin (Methylisooctinylamine) in the treatment of headache. Amer. Pract., 4:31 (Jan.) 1953.
13. Blumenthal, L. S.; Fuchs, M.; and Bennett, Alice: Headache clinic V.: Tension headache. Amer. Pract., 4:701 (Oct.) 1953.
14. Bowen, Ralph: Allergy in identical twins. J. Allergy, 24:236 (May) 1953.
15. Brown, E. A.: A history of allergy (special article). Quart. Review of Allergy and App. Immun., 7:344 (Sept.) 1953.
16. Brown, E. A.: Drug allergy (special article). Quart. Rev. of Allergy and App. Immun., 7:51 (March) 1953.
17. Brown, E. A.: Sensitivity to grape and grape products, including wine. Ann. Allergy, 11:590 (Sept.-Oct.) 1953.
18. Brown, C.; Propp, S.; Guest, C. M.; Beebe, R. T.; and Early, L.: Fatal fungus infections complicating antibiotic therapy. JAMA, 152:206 (May) 1953.
19. Burman, H.: Treatment of common skin disorders. Med. Clin. NA, 37:1175 (July) 1953.
20. Cabasso, V. J.; and Hoagland, R. J.: Mumps skin test during a mumps epidemic. JAMA, 152:1527, 1953.
21. Chemical laboratory report: A study of cigarettes, cigarette smoke and filters. 1. Filter tip cigarettes. JAMA, 152:917 (July) 1953.
22. Chobot, R.: Comment on forum question. Modern Medicine, 22:170 (Jan.) 1954.
23. Clawson, R. A.: Treatment of severe migraine with cafergot. Rocky Mt. Med. Jour., 49:1038 (Dec.) 1952.
24. Coggins, R. P.; Skinner, J. M.; and Burrell, Z. L.: Anaphylactoid reactions to sodium dehydrocholate. New Eng. J. Med., 249: 154 (July) 1953.
25. Cohen, A. L.: Arachnidism. J. Allergy, 24:369 (July) 1953.
26. Cohen, V. L.; and Osgood, H.: Disability due to inhalation of grain dust. J. Allergy, 24:193 (May) 1953.
27. Collins-Williams, C.; and Vincent, J.: Sensitivity reactions to penicillin in children. Ann. Allergy, 11:459 (July-Aug.) 1953.
28. Criep, Leo H.: The role of the general practitioner in the treatment of allergy. Amer. Pract., 4:546 (Aug.) 1953.
29. Criep, Leo H.: The management of the allergic child. Penn. M. J., 56:433, 1953.
30. Criep, Leo; and Ribeiro, C.: Allergy to procaine hydrochloride with three fatalities. JAMA, 151:1185 (April) 1953.
31. Crissey, J. T.; and Coccamise, C. W.: Antibiotic drug eruptions. New York J. Med., 53:2085, 1953.
32. Croxatto, O. C.: The failure of histamine to reproduce the Arthus phenomenon. Bull. Johns Hopkins Hospital, 90:439, 1952.
33. DeBold, F. F.; and Fox, L. A.: Sensitivity to intravenous procaine. Three case reports. Ann. Allergy. 11:778 (Nov.-Dec.) 1953.
34. Dixon, F. J.: The use of I^{131} in immunologic investigation. J. Allergy, 24:547 (Nov.) 1953.
35. Editorial: JAMA, 154:412 (Jan.) 1953.
36. Editorial: J. Allergy, 24:379 (July) 1953.
37. Editorial: Ann. Allergy, 11:781 (Nov.-Dec.) 1953.
38. Editorial: JAMA, 154:340 (Jan.) 1954.
39. Editorial: J. Allergy, 24:474 (Sept.) 1953.
40. Feinberg, A. R.: The antihistamines in treatment of allergic diseases. Postgrad Med., 13:266 (Mar.) 1953.
41. Fond, I. A.: Piromen therapy in asthma. J. Allergy, 24:326 (July) 1953.
42. Fowler, E. R., Jr.: Intravenous procaine in treatment of Ménière's disease. Ann. Otol., Rhinol., and Laryng., 62:1186, 1953.
43. Frankland, A. W.: Locust sensitivity. Ann. Allergy, 11:445 (July-Aug.) 1953.
44. Friedell, M. T.: Effect of cigarette smoke on the peripheral vascular system. JAMA, 152:897 (July) 1953.
45. Fries, J. H.; and Borne, S.: Remission of intractable allergic symptoms by acute intercurrent infections. Ann. Int. Med., 38:928 (May) 1953.
46. Fuller, C. J.: Farmer's lung. A review of present knowledge. Thorax (London), 8:59 (Mar.) 1953.

47. Furmanski, A. R.: Histamine therapy in acute ischemia of the brain. Arch. Neurol. and Psychiat., 69:104, 1953.
48. Garvey, J. L.: Serum neuritis: Twenty cases following use of antitetanic serum. Postgrad. Med., 13:210 (Mar.) 1953.
49. Gaul, L. E.: Metal sensitivity in eczema of the hands. Ann. Allergy, 11:758 (Nov.-Dec.) 1953.
50. Glaser, J.; and Johnstone, D. E.: Prophylaxis of allergic disease in the newborn. JAMA, 153:620 (Oct.) 1953.
51. Glaser, J.: Comment on forum question. Modern Medicine, 22:172 (Jan.) 1954.
52. Goehring, W. O.; and Grant, J. J.: Allergic reaction to streptokinase-streptodornase solution given intrapleurally. JAMA, 152:1429 (Aug.) 1953.
53. Halpin, L. J.: Bell's palsy, serum or penicillin sensitivity? A case report. Ann. Allergy, 12:196 (Mar.-Apr.) 1954.
54. Harkavy, J.; and Perlman, E.: Allergy and prolonged illness. Med. Clin. NA, 37:767 (May) 1953.
55. Harrison, Mary; and Mercer, R. D.: Vitamin A intoxication. Clev. Clin. Quart., 20:424 (Oct.) 1953.
56. Heck, F. J.: The influence of drugs on blood and bone marrow. Postgrad. Med., 13:185 (Mar.) 1953.
57. Henderson, L. L.; Prickman, L. E.; Koelsche, G. A.; Carryer, H. M.; and Peters, G. A.: Diagnosis and management of hay fever. Proc. Staff Meetings of the Mayo Clinic, 28:497 (Sept.) 1953.
58. Herrell, W. E.: Reactions of toxicity incident to antibiotic therapy and their management. Ann. Allergy, 11:555 (Sept.-Oct.) 1953.
59. Hollender, A. R.: Regrowth of nasal polyps. Eye, Ear, Nose and Throat Month., 32:635, 1953.
60. Holman, J.: Comment on forum question. Modern Medicine, 22:172 (Jan.) 1954.
61. Hunnicutt, L. J.: The chronically congested nose. Bull. Vancouver Med. Assoc., 28:348 (July) 1952.
62. Kahn, I.: Comment on forum question. Modern Medicine, 22:168 (Jan.) 1954.
63. Kaufman, William: Food-induced allergic musculoskeletal syndromes. Ann. Allergy, 11:179 (Mar.-Apr.) 1953.
64. Kern, R. A.: Allergic states and the cardiovascular system. Med. Clin. NA, 37:1625 (Nov.) 1953.
65. Kerr, A.; and Derbes, V. J.: The syndrome of cough scyncope. Ann. Int. Med., 39:1240 (Dec.) 1953.
66. Kesten, B. M.; and Slatkin, M.: Diseases related to light sensitivity. Arch. Derm. and Syph., 67:287 (Mar.) 1953.
67. Kierland, Robert: Physical allergies. Arch. Derm. and Syph., 68:61 (July) 1953.
68. Koffler, Arthur: Allergic skin reaction to procaine amide hydrochloride. JAMA, 152:28 (May) 1953.
69. Krieger, H. and others: The use of radioactive iodinated human serum albumin in evaluating peripheral circulation. Ann. Surg., 136:357 (Sept.) 1952 (quoted by Friedell).
70. Kunstadtker, R. H. and Schultz, A.: Gastrointestinal allergy and the celiac syndrome with particular reference to allergy to cow's milk. Ann. Allergy, 11:426 (July-Aug.) 1953.
71. Kurtz, G. I.: The relief of allergic disorders with a soluble calcium and phosphate salt. J. Med. Soc. New Jersey, 50:308 (July) 1953.
72. Kutcher, A. H.; Budowsky, J.; Love, S. L.; and Chilton, N. W.: Reactions following the use of aureomycin and procaine penicillin troches: a controlled study. J. Allergy, 24:164 (Mar.) 1953.
73. Lanzarat, M. M.: Changes in the electrocardiogram seen during attacks of migraine and their normalization by ergotamine tartrate administration. Ann. Allergy, 11:24 (Jan.-Feb.) 1953.
74. Larsen, E. A.: Anaphylactic shock due to penicillin. J. Iowa State Med. Soc., 43:217 (June) 1953.
75. Larson, R. K.: Mechanism of quinidine purpura. Blood, 8:16, 1953.
76. Laub, G. R.: Ménière's disease. Case report and discussion. Ann. Allergy, 11:190 (Mar.-Apr.) 1953.
77. Lewis, G. M.; Hopper, M. E.; and Scott, M. J.: Generalized trychophyton rubrum infection associated with systemic lympoblastoma. Arch. Derm. and Syph., 67:247 (Mar.) 1953.

78. Lewy, R. B.: A critical evaluation of medical and surgical therapy of Ménière's disease. Amer. Pract., 4:534 (Aug.) 1953.
79. Livingston, S. F. and Harten, M.: The absorption of antigen from the mammary ducts. J. Allergy, 24:258 (May) 1953.
80. Lowell, F. C.: The prevention and treatment of drug allergies. Med. Clin. of NA, 37:1409 (Sept.) 1953.
81. McCorriston, L. R.: Piromen treatment of varied dermatoses. The Canad. Med. Assoc. Jour., 68:137, 1953.
82. McGeachy, T. E. and Bloomer, W. E.: Phenobarbitol sensitivity syndrome. Amer. J. Med., 14:600, 1953.
83. Magee, K. R.; Westerberg, Martha; and DeJong, R. N.: Treatment of headache with ergotamine-caffeine suppositories. Neurology, 2:447 (Nov.-Dec.) 1952.
84. Martarelli, J.: Allergy to brucellosis. Int. Arch. Allerg., 4:335, 1953.
85. Mayer, P. S.; Mosko, M. M.; Schutz, P. J.; Osterman, F. A.; Steen, L. H.; and Baker, L. A.: Penicillin anaphylaxis. J.A.M.A., 151:351, 1953.
86. Meakins, J. C.: "Cardiac asthma." Postgrad. Med. 13:89 (Feb.) 1953.
87. Miller, F. L. and Walker, R.: The clinical toxicity of terramycin. New Eng. J. Med., 249:479, 1953.
88. Minns, J. F.: Allergic conditions of lids, conjunctiva and cornea. Mod. Medicine, 22:85 (Jan.) 1954.
89. Mueller, H. L. and Hill, L. W.: Allergic reactions to bee and wasp stings. New Eng. J. Med., 249:726, 1953.
90. Naranjo, P. and Naranjo, E.: Inactivation of the antihistaminic drugs in the liver and in the gastrointestinal tract. J. Allergy, 24:442 (Sept.) 1953.
91. Nathan, D. A.; Meitus, M. L.; Capland, L.; and Lev, M.: Death following phenyl-butazone (Butazolidin) therapy. Report of case. Ann. Int. Med., 39:1096 (Nov.) 1953.
92. Nelson, L. S. and Stoesser, A. V.: Cleansing agents. Irritating and non-irritating to the skin. Ann. Allergy, 11:572 (Sept.-Oct.) 1953.
93. Nikishin, I. F.: Anaphylactic shock following administration of penicillin. Ohio State Med. Jour., 49:305, 1953.
94. Ogden, Henry: Headache and tension. Ann. Allergy, 11:329 (May-June) 1953.
95. O'Hare, J. M.; Shapiro, M. W.; and Creeden, F. V.: Fatal reaction following intravenous 10 per cent dextrose. Amer. J. Surg., 85:658, 1953.
96. O'Leary, P. A. and Erickson, J. G.: Use and abuse of cortisone and corticotropin (ACTH) in dermatology. J.A.M.A., 152:1695 (Aug) 1953.
97. Osgood, E. E.: Hypoplastic anemias and related syndromes caused by drug idiosyncrasy. J.A.M.A., 152:816 (June) 1953.
98. Osgood, E. E.: Drug induced hypoplastic anemias. Ann. Int. Med., 39: 1173 (Dec.) 1953.
99. Pensky, N. and Goldberg, N.: Treatment of refractory acne with a fractionated type of liver extract. N. Y. State Jour. Med., 53:2238 (Oct.) 1953.
100. Peters, G. A.: Migraine: diagnosis and treatment with emphasis on the migraine-tension headache, provocative tests and the use of rectal suppositories. Proc. Staff Meeting Mayo Clinic, 28:673 (Dec.) 1953.
101. Piraino, A. F.: Schonlein-Henoch syndrome, with report of a case. Ann. Allergy, 11:332 (May-June) 1953.
102. Pittman, Helen: Bronchiectasis. Med. Clin. NA, 37:1351, 1953.
103. Queries and minor notes: J.A.M.A., 152:105 (May) 1953.
104. Queries and minor notes: J.A.M.A., 152:1392 (Aug.) 1953.
105. Queries and minor notes: J.A.M.A., 152:104 (May) 1953.
106. Questionnaire: Internat. Corres. Soc. of Allergists, Series 16, Pages 29-40, 1953.
107. Questionnaire: Internat. Corres. Soc. of Allergists, Series 16, Pages 44, 51 and 68, 1953.
108. Rackemann, F. M.: Long-range care of allergic children. Med. Clin. N.A., 37:1419 (Sept.) 1953.
109. Ratner, B. and Silberman, D. E.: Critical analysis of the hereditary concept of allergy. J. Allergy, 24:371 (July) 1953.
110. Ratner, B.: Comment on forum question. Modern Med., 22:164 (Jan.) 1954.
111. Reyer, W. A.: Exacerbation of ivy dermatitis by rhus antigen injections. Ann. Allergy, 11:91 (Jan.-Feb.) 1953.

112. Reicher, J.: The importance of the specific allergen. A case report. Ann. Allergy, 11:12 (Jan.-Feb.) 1953.
113. Reichlin, S.; Loveless, M.; and Kane, E. G.: Loeffler's syndrome following penicillin therapy. Ann. Int. Med., 38:113 (Jan.) 1953.
114. Robison, W. P. and Moss, B. F.: Treatment of Bell's palsy with cortisone. J.A.M.A., 154:142 (Jan.) 1954.
115. Rook, Arthur and Frain-Bell, W.: Papular urticaria. Arch. Dis. Ch., 28:304 (Aug.) 1953.
116. Rose, Bram: Panel discussion on allergic reactions to penicillin. J. Allergy, 24:383 (Sept.) 1953.
117. Rosen, F. L.: Comment on forum question. Modern Medicine, 22:164 (Jan.) 1954.
118. Rost, G. S.: Allergic reactions to catgut preservatives. J. Iowa State Med. Soc., 43:218 (June) 1953.
119. Rostenberg, Adolph: The Shwartzman phenomenon: a review with a consideration of some dermatological manifestations. The Brit. Med. Jour. of Derm., 65:389 (Nov.) 1953.
120. Rowe, A. H.; Rowe, A. H., Jr.; and Uyeyama, K.: Regional enteritis. Its allergic aspects. Gastroenterology, 23:554, 1953.
121. Samter, M.; Hall, B.; and Palicke, R.: Studies of idiosyncrasy to acetyl salicylic acid and related drugs. In press—paper presented at Regional Meeting, ACP, Milwaukee, Wis. (Nov.) 1953.
122. Schiller, I. W.: Edit of panel on allergic reactions to penicillin. J. Allergy, 24:383 (Sept.) 1953.
123. Sherman, W. B.: Panel discussion on allergic reactions to penicillin. J. Allergy, 24:383 (Sept.) 1953.
124. Siegal, S.; Steinhardt, R. W.; and Gerber, R.: Fatal and near-fatal penicillin anaphylaxis. Three new cases with a note on prevention. J. Allergy, 24:1 (Jan.) 1953.
125. Small, J. C. and Small, J. C., Jr.: Bacterial allergy in the rheumatic diseases. Ann. Allergy, 11:609 (Sept.-Oct.) 1953.
126. Smith, S. F.: The headache problem. J. Med. Soc. N. J., 50:138 (Apr.) 1953.
127. Sobel, Gertrude: Adenotonsillectomy and its relation to asthma. Ann. Allergy, 11:583 (Sept.-Oct.) 1953.
128. Solval, A. R.: Severe immediate constitutional reaction to penicillin. J.A.M.A., 152:1430, 1953.
129. Spain, W. C.: The immunologic aspects of allergic conditions. Ann. Int. Med., 38:188 (Feb.) 1953.
130. Spielman, A. D.: Sensitivity to corn starch. A case report. J. Allergy, 24: 522 (Nov.) 1953.
131. Steinhardt, M. J. and Fisher, G. S.: Cold urticaria and purpura as allergic aspects of cryoblobulinemia. J. Allergy, 24:335 (July) 1953.
132. Sterling, A.: Anaphylactic shock following penicillin therapy in bronchial asthma. J. Allergy, 24:542 (Nov.) 1953.
133. Stevens, F. A.: Sensitization of nasal mucous membranes to bacteria. J. Allergy, 24:446 (Sept.) 1953.
134. Stevens, F. A.: Acute asthmatic episodes in children caused by upper respiratory bacteria, during colds with or without sensitization. J. Allergy, 24:221 (May) 1953.
135. Studdert, T. C.: Farmer's lung. Brit. Med. Jour., 1305 (June) 1953.
136. Swinny, Boen: Personal communication.
137. Swinny, Boen: Allergic parotitis. Ann. Allergy, 11:473 (July-Aug.) 1953.
138. Tachau, Paul: Atopic dermatitis in the infant. (Infantile eczema). Postgrad. Med., 13:252 (Mar.) 1953.
139. Theodore, F. H.: Drug sensitivities and irritation of the conjunctiva. J.A.M.A., 151:25, 1953.
140. Thomas, L. and Good, R. A.: Studies on the generalized Shwartzman reaction. I. General observations concerning the phenomenon. J. Exper. Med., 96: 605, 1952.
141. Thomas, L. and Good, R. A.: The effect of cortisone on the Shwartzman reaction. The production of lesions resembling the dermal and generalized Shwartzman reactions by the single injection of bacterial toxin in cortisone treated rabbits. J. Exper. Med., 95:409, 1952.
142. Thomas, J. W.: Education and advancement in allergy. J. Allergy, 24:254 (May) 1953.
143. Thompson, H. E. and Rowe, H. J.: A case of hypoplastic anemia with secondary thrombocytopenic purpura following the use of chloramphenicol. Ann. Int. Med., 39:1124 (Nov.) 1953.

144. Tunis, M. M. and Wolff, H. G.: The treatment of headache. Med. Clin. N.A., 37:1251 (July) 1953.
145. Unger, L. and Unger A.: Trypsin inhalations in respiratory conditions with thick sputum. J.A.M.A., 152:1109 (July) 1953.
146. Unger, L. and Unger, A.: The use of Tryptar (trypsin) in bronchial asthma and other conditions. Ann. Allergy, 11:494 (July-Aug.) 1953.
147. Van Scott, E. J. and Lyon, J. B.: A chemical measure of the effect of soaps and detergents on the skin. Jour. Invest. Derm., 21:199, 1953.
148. Waldbott, George: Further observations on smoker's respiratory syndrome. Ann. Int. Med., 39:1026 (Nov.) 1953.
149. Wall, J. W. and Shure, N.: Intranasal cortisone. Arch. Otolaryng., 56:172, 1952.
150. Walsh, J. R. and Zimmerman, H. J.: Demonstration of the "L.E." phenomnon in patients with penicillin hypersensitivity. Blood, 8:65 (Jan.) 1953.
151. Watkins, A. L.: Serum neuritis. Arch. Phys. Med. and Rehab., 34:231, 1953.
152. Weiss, L. R.: Anaphylactic reaction from topical penicillin. J. Allergy, 24:407 (Sept.) 1953.
153. Welch, H. and co-workers: Quoted in Editorial, Ann. Allergy.
154. Wittich, F. W.: The impact of allergy on general medicine. Acta Allergologica, 6:1, 1951.
155. Wofford, C. P.: Anaphylaxis to penicillin. Ann. Allergy, 11:470 (July-Aug.) 1953.
156. Wolf, A. F.; Bailey, H. A.; and Coleman, J. M.: Allergy to endogenous hormones. Ann. Allergy, 11:78 (Jan.-Feb.) 1953.
157. Wolff, H. G.; Tunis, M. M.; and Goodell, H.: Studies on headache. Arch. Int. Med., 92:478, 1953.

FIRST BRAZILIAN CONGRESS OF MILITARY MEDICINE

Dr. Marques Porto, President of the Brazilian Academy of Military Medicine, announces that the First Brazilian Congress of Military Medicine will take place in Sao Paulo, Brazil, July 11 to 15, 1954, under the auspices of the Commission of the Fourth Centenary of Sao Paulo. This congress will include doctors, dentists, and pharmacists, both civil and military, and a commemorative medal will be given to effective members. Subjects to be dealt with will include medicine, surgery, pharmacy, odontology, organization, and administration.

Convention Echoes

PROCEEDINGS OF THE DECENNIAL CONGRESS

The Decennial Congress of the College was held at the Roney Plaza Hotel, Miami Beach, Florida, April 5 to 10, 1954. The scientific program was preceded by the customary intense Graduate Instructional Course, April 5 to 7. Through the untiring efforts of Dr. Ethan Allan Brown, Chairman, and Dr. Hal M. Davison, Co-Chairman, of the Instructional Course, an unprecedented course was held, including everything for the student of allergy, as well as for those who desire a refresher course. There were 170 registrants. The guest speakers for the course were Dr. Hans Selye, Montreal, who was also Chairman of the Monday Evening Panel on The Steroid Hormones; Dr. Alvan L. Barach, New York; Dr. Homer F. Marsh, Miami. There were thirty-six technical exhibits of products related to allergy and allied subjects. There were five scientific exhibits. During the entire meeting Dr. Stephen D. Lockey and Associates conducted an exhibit on Office and Laboratory Procedures.

All of the Committee meetings were held on Tuesday. There were evening Panels the three evenings during the course; Monday evening, The Steroid Hormones and Pediatric Panel, Allergy in the Infant Under Two; Tuesday evening, Antihistaminic Agents and Mold Allergy; Wednesday evening, Any Questions? and Emotional Factors in Allergic Disorders.

The Congress opened on Thursday, April 8, with a General Session of miscellaneous papers. Dr. Giles A. Koelsche, Over-All Chairman of the Program Committee, presided at the morning General Session. The morning session was followed by a Round Table Luncheon with Dr. J. Warrick Thomas, Moderator. The subject was "Pitfalls in the Diagnosis and Management of Asthma." Thursday afternoon, Dr. Mayer A. Green, Pittsburgh, was in the chair. There was a very cordial cocktail hour that evening, courtesy of the Schering Corporation, Bloomfield, New Jersey, followed by a banquet, entertainment and dancing.

Friday morning Dr. Jerome Glaser, Rochester, New York, presided over a section on Pediatric Allergy. At noon there was a Round Table Luncheon on Pediatric Allergy with Dr. C. Collins-Williams, Toronto, Ontario, as Moderator. There was also a Round Table Luncheon on Otorhinolaryngologic Allergy, Dr. Lawrence K. Gundrum, Los Angeles, Moderator.

Friday afternoon Dr. M. Murray Peshkin gave his Presidential Address. He was introduced by Dr. Homer E. Prince, President-Elect. The guest speaker was Dr. John W. Gowen, Professor of Genetics, Iowa State College of Agriculture and Mechanic Art, Ames, Iowa, whose subject was "Individuality as a Factor in Resistance to Disease." At 3:30 p.m. there was an enthusiastic Business Meeting at which time Dr. Homer Prince gave his presidential acceptance address. Friday evening there was a Dermatologic Allergy Session, over which Dr. Adolph B. Loveman, Louisville, Kentucky, presided. This was followed by a Round Table Discussion. Also, the same evening, there was a Clinical Panel on Psychosomatic

Allergy, at which the Moderators from each workshop of Wednesday evening on Emotional Factors in Allergic Disorders summarized their findings. Dr. Hyman Miller, Beverly Hills, California, was Moderator.

Saturday morning there was a Section on Ophthalmic Otorhinolaryngologic Allergy, presided over by Dr. Hugh A. Kuhn.

The first meeting of the Board of Directors, with Dr. M. Murray Peshkin as Chairman, was held Sunday morning, April 4, at 8:00 a.m., followed by the first Board of Regents meeting. The new Board of Regents meeting was held Saturday morning, April 10, with Dr. Homer E. Prince, President, in the chair.

At the Annual Business Meeting in the Surf Room, the following officers were elected:

President—Homer E. Prince, M.D., Houston, Texas
President-Elect—Lawrence J. Halpin, M.D., Cedar Rapids, Iowa
First Vice President—George L. Waldbott, M.D., Detroit, Michigan
Second Vice President—Rudolf L. Baer, M.D., New York, New York
Executive Vice President and Counsel—Eloi Bauers, Minneapolis, Minn.
Secretary-Treasurer—Fred W. Wittich, M.D., Minneapolis, Minn.
Board of Regents—Three-year Term:
Susan C. Dees, M.D., Durham, North Carolina
James A. Mansmann, M.D., Pittsburgh, Pennsylvania
James E. Stroh, M.D., Seattle, Washington

The present Board of Regents, therefore, consists of the following:

	Term Expires
Harry S. Bernton, M.D., Washington, D. C.	1955
Susan C. Dees, M.D., Durham, North Carolina	1957
Vincent J. Derbes, M.D., New Orleans, Louisiana	1955
Jerome Glaser, M.D., Rochester, New York	1956
Morris A. Kaplan, M.D., Chicago, Illinois	1956
Giles A. Koelsche, M.D., Rochester, Minnesota	1956
James A. Mansmann, M.D., Pittsburgh, Pennsylvania	1957
L. Everett Seyler, M.D., Dayton, Ohio	1955
James E. Stroh, M.D., Seattle, Washington	1957
Homer E. Prince, M.D. (President), Houston, Texas	1955

Dr. F. W. Wittich, Secretary-Treasurer, presented a complete financial report for the year ending December 31, 1953.

The first annual meeting of the Board of Regents was held Sunday morning, April 4, 1954, Dr. M. Murray Peshkin presiding. Pursuant to legal requirements, an amendment which had appeared in the January-February, 1954, ANNALS OF ALLERGY, was recommended for favorable action by the Board of Directors and proposed to the Board of Regents. A motion was carried unanimously that the second sentence of the first paragraph of Article V, Section 7, Subdivision i entitled, "Board of Directors," be deleted and replaced by the following sentence, "The Board of Directors is always composed of the following officers: The retiring President, who shall be its Chairman; the incumbent President, who shall be its Vice Chairman; the President-Elect, the first Vice President, and the Secretary-Treasurer."

It was also moved, seconded and unanimously passed that as a corollary to this amendment, Article V, Section 7, Subdivision f, entitled, "The Secretary-Treasurer" be amended by deleting therefrom the sentence which reads as follows: "He shall be an *ex officio* member of all committees and boards."

Following recommendations of the interim meeting of the Board of Directors, an amendment to Article V, Section 7, Subdivision g, entitled "Nominations of Officers" was proposed and published according to the bylaws more than thirty (30) days prior to this meeting, in the January-February, 1954, ANNALS OF ALLERGY. The changes in the bylaws in question and the amendment proposed by the Board of Directors subsequently published in this issue of the ANNALS OF ALLERGY was adopted as read. This new amendment of the bylaws which had been adopted and declared now in effect, defines the next nominating committee to be selected to be composed of five (5) members, the President, two (2) members of the Board of Regents, each of whom at the time of selection shall have served at least two years on the Board, and two (2) past Presidents to be selected by the Board. This nominating committee was not selected until the meeting of the new Board which was held on Saturday morning, April 10, 1954. According to the resolution adopted by the Board of Regents at its annual meeting on the previous Sunday, Dr. Homer Prince automatically becomes Chairman of the Nominating Committee, as the new President, with Drs. Harry S. Bernton, Vincent J. Derbes and L. Everett Seyler, also members. The other two members are Drs. Hal M. Davison and J. Warrick Thomas. After some discussion it was felt advisable that this committee not function earlier than three months after its selection and was to have the benefit of any and all data and information on file in the Secretary's office with respect to the qualifications, fitness, capacity, standing, and accomplishments in the field of allergy of those whom this committee might consider for selection on the official slate, that it was intended that the Nominating Committee shall not have any sessions or function during the week of the convention and that its deliberations shall be later and by correspondence.

The Finance Committee will meet at the same time as the Board of Directors' interim meeting. Members of the Finance Committee are: Dr. John Mitchell, Chairman, one year; Dr. Harold Abramson, two years; and Dr. J. Warrick Thomas, three years.

The Over-all Chairman of the Program Committee for the ensuing year is Dr. Lawrence J. Halpin. Dr. Orval R. Withers was appointed Chairman of the Instructional Course, with Dr. Morris A .Kaplan, Co-Chairman. Dr. Giles A. Koelsche was appointed as Consultant to the Program Committees. Dr. Leon Unger is Chairman of the Local Arrangements Committee. According to the bylaws, the Program Committee consists also of the President and the Secretary-Treasurer.

The Eleventh Annual Congress and Graduate Instructional Course will be held at the Morrison Hotel, Chicago, April 25-30, 1955.

WOMEN'S AUXILIARY OF THE AMERICAN COLLEGE OF ALLERGISTS

On April 5, 1954, at the Decennial Congress of the American College of Allergists, Inc., the Board of Regents, by appropriate resolution, took definite action to make possible the establishment of a Women's Auxiliary, as an independent legal entity, to work very closely with, and to complement wherever possible, the functions of the American College of Allergists.

On April 8, 1954, The Women's Auxiliary of the American College of Allergists, Inc., was formed. The following officers were elected for a two-year term:

President—Mrs. Morris A. Kaplan, Chicago, Illinois
President-Elect—Mrs. Ethan Allan Brown, Boston, Massachusetts
Vice President—Mrs. Fred W. Wittich, Minneapolis, Minnesota
Secretary—Mrs. J. Warrick Thomas, Richmond, Virginia
Treasurer—Mrs. Boen Swinny, San Antonio, Texas
Historian—Mrs. Lester L. Bartlett, Pittsburgh, Pennsylvania

Board of Governors

Three-Year Term

Mrs. Homer E. Prince, Houston, Texas
Mrs. Lawrence Halpin, Cedar Rapids, Iowa
Mrs. Lester L. Bartlett, Pittsburgh, Pennsylvania

Two-Year Term

Mrs. L. O. Dutton, El Paso, Texas
Mrs. Orval Withers, Kansas City, Missouri
Mrs. David Thomas, Jr., Augusta, Georgia

One-Year Term

Mrs. Leon Unger, Chicago, Illinois
Mrs. M. Murray Peshkin, New York, New York
Mrs. Johnny A. Blue, Oklahoma City, Oklahoma

Drs. Walker L. Rucks, Memphis, Tennessee, L. O. Dutton, El Paso, Texas, and Lester L. Bartlett, Pittsburgh, Pennsylvania, were selected to act as liaison contacts between the College and the Auxiliary. (Two-year term).

The Annual meeting of the Women's Auxiliary shall be held at the same time, and in the same city, and concurrently with the Annual meeting of The American College of Allergists, Inc.

Membership shall be composed of two classes: voting members and non-voting members. Each class shall enjoy the same rights and privileges, excepting only the right to vote at meetings, and to hold office, which rights and privileges shall be confined to voting members. The wives and widows of Active and Associate Fellows in good standing, shall be eligible to become voting members. The wives of honorary and sustaining members shall be eligible to become non-voting members. Initial fee is five dollars ($5.00), and the Annual dues are five dollars ($5.00), both payable in advance.

Charter Membership shall be limited to those joining the organization within one year from date of organization. YOU ARE ALL INVITED TO BECOME CHARTER MEMBERS. Send your check for ten dollars ($10.00) to Mrs. Boen Swinny, 143 Bluebonnet Blvd., San Antonio 9, Texas. Make it payable to Women's Auxiliary, American College of Allergists, Inc., Eunice Swinny, Treasurer.

In Memoriam

WILLEM KREMER

It was with deep regret that we received word of the death on May 7, 1954, of Dr. Willem Kremer, of Amsterdam, Netherlands. He was sixty-four years of age.

Dr. Kremer was president of the Netherlands Allergy Society (Nederlandse Vereniging voor Allergie) and was a member of the Constitution and By-Laws Committee of the First Congress of the International Association of Allergology.

Just a year previous to his death, Professor Kremer presided at the second annual meeting of the Netherlands Association of Allergy, which was held in Utrecht and Groningen, May 14-16, 1953. At this time, he presided at a round-table meeting and gave a welcoming address to a group of scientists from all parts of the world who were also attending the Second European Congress on Allergology at Copenhagen. All the registrants at this meeting visited the Amsterdam Clinics of Allergic Diseases, of which Dr. P. J. van der Werff is the general director. This clinic was the original clinic of Dr. W. S. van Leeuwen, who in 1924 published an article on "Bronchial Asthma in Relation to Climate," and a year later with Dr. Kremer, Z. Bien, and H. Varekamp reported molds as a cause of bronchial asthma. It was at this clinic that the first allergen-proof chamber, still in use, was designed.

At the Amsterdam meeting last year, Dr. and Mrs. Kremer gave an informal reception to those visiting the clinic, and Dr. Kremer was at his very best, giving a delightful reminiscing talk on the development of the Amsterdam Clinics of Allergic Diseases.

Dr. Kremer led a very happy family life, and enjoyed his children and grandchildren. He will long be remembered as one of the outstanding allergists of our time, a sincere student of medicine, and a fine gentleman.

News Items

SECOND INTERNATIONAL CONGRESS OF ALLERGOLOGY

Plans are well under way for the Second Congress of the International Association of Allergology, comprising twenty-eight countries, to be held at the Hotel Quintandinha in Rio de Janeiro, Brazil, November 6-12, inclusive, 1955. The Program Committee is arranging a program, with the approval of the Organizing Committee of the Brazilian Allergy Society, which includes Nobel Prize winners and other outstanding scientists as guest speakers. There will also be many plenary sessions at which papers of ten minutes' length can be presented. The International Business Machine system will be used to present the talks in three languages, English, French and Spanish.

The Brazilian Allergy Society, of which Dr. E. Brum Negreiros is President, and Dr. Ulysses Fabiano Alves, is Secretary-General, together with their committee, has assured us that, through the aid of the Brazilian Federal Government and the Government of the City of Rio de Janeiro, as well as through revenue from the technical and commercial exhibits, they will have adequate facilities for financing the local expenses.

Arrangements have been made through the bankers and Merchants Travel Service, 511 Fifth Avenue, New York 17, N. Y., telephone, Murray Hill 7-6938, to publicize the meeting in North America by sending out a letter, with travel information, through the President of the Association, Dr. F. W. Wittich, with headquarters at 424 LaSalle Medical Building, Minneapolis, Minn. This travel information, prepared for ready reference, outlines the various ways and means of travel to and from Rio de Janeiro. In order to facilitate the travel arrangements for the delegation from the United States the travel agency is asking the various steamship and airlines to set aside a block of accommodations on convenient departures from New York and Gulf ports. Further through air rates from western cities are being prepared and will be available to those from that area. Those who wish to deal directly with the Bankers and Merchants Travel Service should address them at the above New York address. This letter, mailed to allergists in this country, will also contain health and visa requirements for travel in South America and essential requirements for United States citizens when making application for passport. Make application for your passports and visas as early as possible. The Bankers and Merchants Travel Service has offered to arrange for the visas.

Make your reservations early as there is an attendance of at least 1200 expected. There is every reason to expect a deduction from your income tax for those who attend and participate in the programs or discussions. Those with limited incomes can make arrangements with the Pan-American Airlines for a minimum down payment, and monthly payments of the balance until the trip is paid for.

The Brazilian Allergy Society is making elaborate arrangements for entertainment for the wives and other relatives of those attending. Plan on taking your 1955 vacation in November at Rio. Every scientist or physician interested is cordially invited to attend.

AMERICAN FOUNDATION FOR ALLERGIC DISEASES

Formation of a Scientific and Educational Council of nationally known scientists and educators to promote more research and wider professional education in the field of the allergic diseases has been announced by the American Foundation for

Allergic Diseases from national headquarters, 525 Legington Avenue, New York City.

The members are as follows: Robert A. Cooke, M.D., director The Institute of Allergy, Roosevelt Hospital, New York; Frank J. Dixon, M.D., professor of Pathology, University of Pittsburgh Medical School, Pittsburgh, Pa.; Alfred Gilman, Ph.D., professor of Pharmacology, College of Physicians and Surgeons, Columbia University, New York; Elvin A. Kabat, Ph.D., professor of Microbiology, College of Physicians and Surgeons, Columbia University, New York; Richard A. Kern, M.D., professor of Medicine, Temple University Medical School, Philadelphia, Pa.; Giles A. Koelsche, M.D., assistant professor of Medicine, Mayo Foundation Graduate School, University of Minnesota, Rochester, Minn.; John H. Mitchell, M.D., professor of Clinical Medicine, Ohio State University, Columbus, Ohio; Henry Stevens, Ph.D., head of Section on Allergens, Agricultural Research Service, U. S. Department of Agriculture, Washington, D. C.; Cyrus C. Sturgis, M.D., director Simpson Memorial Institute for Medical Research, professor of Medicine, University of Michigan, Ann Arbor, Mich.; Marion B. Sulzberger, M.D., chairman Department of Dermatology and Syphilology, Post-Graduate Medical School, New York University-Bellevue Medical Center, New York.

The American Foundation for Allergic Diseases was established a year ago under the sponsorship of the American Academy of Allergy and the American College of Allergists as a non-profit organization of physicians and laymen to promote allergy research, improve professional education, increase treatment facilities for allergy sufferers, and spread public understanding of the allergic diseases so as to bring about early diagnosis and treatment.

BRAZILIAN SOCIETY OF ALLERGY

The new directory of officials elected for 1954 for the Brazilian Society of Allergy is as follows:

President .....Dr. Eleutherio Brum Negreiros
Vice President .....Dr. Francisco José da Silveira Lobo, Jr.
First Secretary .....Dr. Ulysses Fabiano Alves
Second Secretary .....Dr. Victorio Manoel Savoia
Treasurer .....Dr. Ladislau Somogyi
Librarian .....Dr. Lain Porto de Carvalho

Financial Committee: Dr. Alvaro de Bastos, Dr. Paulo Dias da Costa, Dr. Newton Noli de Moraes.

Alternates: Dr. Creso Castilho Ribeiro, Dr. Afonso Negreiros Sayão Lobato.

POSTGRADUATE COURSE IN PEDIATRIC ALLERGY

The New York Medical College, Flower and Fifth Avenues, Division of Graduate Studies and Department of Graduate Pediatrics, announces a postgraduate course in pediatric allergy under the direction of Bret Ratner, M.D., Professor of Clinical Pediatrics and Associate Professor of Immunology. The course consists of thirty sessions, held on Wednesdays from 9:00 A.M. to 4:00 P.M. from November 3, 1954 to May 25, 1955. The fee for the course is $300. Included in the course will be lecture-seminars, laboratory and clinical procedures, clinic work, ward rounds, and animal experimentation covering basic principles of diagnosis and treatment of allergy in children, and applied immunology. Applicants must be certified in pediatrics or have the requirements for certification. Enrollment is limited. Apply to the office of the Dean, New York Medical College, Fifth Avenue at 106th Street, New York 29, N. Y. A Research Fellowship in Pediatric Allergy is available. Application should be made immediately.

THE EX-PATIENTS' SANATORIUM

The Ex-Patients' Sanatorium for Tuberculosis and Chronic Disease has recently been re-organized and is now accepting applications for the admission of patients with chronic chest diseases. Experience during the past year with cases of Chronic Bronchial Asthma, Pulmonary Fibrosis, and Emphysema has demonstrated the value of institutional management.

The Sanatorium is a free non-sectarian institution located at 8000 East Montview Blvd., in Denver, Colorado, and is equipped with every type of diagnostic and therapeutic facility for the care and treatment of chronic chest diseases. Preferance is given to ambulant and semi-ambulant applicants. Rehabilitation planning for each patient is done through our Social Service Department, though it is recognized that limitations in cardiac and pulmonary reserve may limit the job objectives.

We will welcome your inquiries for the admission of your chronic chest cases for periods from two months to two years or longer, as required.

CALIFORNIA SOCIETY OF ALLERGY

The following officers were elected at a recent meeting of the California Society of Allergy, held during the convention of the California Medical Association, at Los Angeles, California, on May 12, 1954:

President	Norman Shure, M. D. 6317 Wilshire Blvd. Los Angeles, Calif.
President-Elect	Lazarre J. Courtright, M.D. 490 Post Street San Francisco, Calif.
Secretary-Treasurer	Ben C. Eisenberg, M.D. 2680 Saturn Avenue Huntington Park, Calif.

LABORATORY MANUALS AVAILABLE

There are available a few of Dr. Stephen D. Lockey's Manual of Office and Laboratory Procedures which were used at his laboratory course at Miami Beach. The cost of these Manuals is $4.00, plus twenty-five cents for postage. They can be ordered directly from Dr. Lockey at 60 North West End Avenue, Lancaster, Pennsylvania.

DOCTOR EFRON RETIRES

Dr. Bernard G. Efron of New Orleans has retired because of illness. His practice has been taken over by Dr. Stanley Cohen, 1441 Delachaise St., New Orleans. Among other things, Doctor Efron is noted for his development of purified stable extracts. A supply of these extracts is available to allergists. These include extracts of foods, pollens and molds. Orders may be placed through Doctor Cohen at his address.

BOOK REVIEWS

DRUG ADDICTION AMONG ADOLESCENTS, Conferences on. Held at the New York Academy of Medicine November 30, 1951 and March 13 and 14, 1952. Sponsored by the Committee on Public Health Relations of the New York Academy of Medicine, with the assistance of The Josiah Macy, Jr., Foundation. 320 pages. New York and Toronto: The Blackiston Company, 1953. Price $4.00.

The list of contributors to the Conferences represents outstanding professional men in the fields of religion, law, public health and welfare agencies, various medical specialties, leaders in education, and others. The preface by Dr. Hubert S. Howe, Chairman, Subcommittee on Narcotics, Committee on Public Health Relations, The New York Academy on Medicine, states the purpose of these conferences was to obtain the thinking of authorities in medical, psychiatric, sociologic, educational and law-enforcement fields. There is an introduction by Dr. Frank Fremont-Smith, Medical Director, The Josiah Macy, Jr., Foundation.

The First Conference on Drug Addiction Among Adolescents was held at the New York Academy of Medicine on November 30, 1951, under the chairmanship of Dr. Howe. Dr. Howard R. Craig, as Director of the Academy, opened the conference. Names of the discussants and their remarks are reported in detail. The conferences broadly considered the variety of responses to drugs among adolescents, ranging from immediate and sustained rejection, through provisional experimentation, to regular use and addiction. These constitute the various patterns of behavior in relation to drug use, some of which would be lost to view as distinctive patterns were one to focus solely on the addict. Discussions were confined to the experiences of the adolescent up to the time he identifies himself as an addict. Attention was centered on orientation, initiation, and experimentation, evidences of addiction are described, and the analysis of drug behavior was presented in detail and discussed by authorities on the subject.

The Second Conference considered the physiologic action of the opium alkaloids and related drugs, and resulted in a medical prevention program of much promise. A review of the discussions reveals the tremendous prevalence of drug addiction in our social structure. To have these scientists devote so much time to the subject seems to presage a better future for the handling and restoration of this group in society.

There is a glossary of terms used by the addict and an index of subjects and authors.

—I. W.

YEAR BOOK OF DRUG THERAPY. 1953-1954 Year Book Series. Edited by Harry Beckman, M.D., Director Departments of Pharmacology, Marquette University Schools of Medicine and Dentistry, Milwaukee, Wis. 538 pages. Chicago: The Year Book Publishers, 1954. Price $6.00.

This 1953-1954 Year Book Series accomplishes its purpose. The many noteworthy worldwide advances of diagnostic and therapeutic procedures in cases most frequently encountered in this field of practice are presented. This new series indicates publication begins September 1953 with the publication of the Year Book of Medicine and ends in May 1954 with the Year Book of Pathology and Clinical Pathology. The 1953-1954 series volume is, therefore, the immediate sequel to the 1952 volume and covers twelve months' literature without interruption or intermission.

Up-to-date developments with regard to antibiotics are completely evaluated. Anticoagulant therapy in congestive heart failure also receives attention, as well as the new theophylline preparation.

The new adrenergic blocking agents are discussed, as well as the use of hydergine in malignant hypertension. Up-to-date methods of therapy with ACTH and cortisone and other therapeutic measures reveal the vast grasp of the authors in the field of therapy.

The subjects are listed alphabetically, which brings allergy into a prominent position. The new developments in the antihistamine field and the role of ACTH and cortisone in the treatment of allergic diseases are presented. There is an excellent classification of drugs used in treating allergies which may produce idiosyncrasy causing hypoplastic anemia or related syndromes. The chapter on antibiotics and sulfonamides is quite complete. The more recent therapy in cardiovascular disease takes up twenty-seven pages of the book. The latest developments in the fields of dermatology, neoplastic diseases, as well as treatment of pain, peptic ulcer, poisoning, rheumatic disorders, colitis and enteritis, neuropsychiatry, ophthalmology, pediatrics, surgery and venereology are given excellent consideration. There is a complete index. The binding, printing and paper stock are of high quality.

THE MEDICAL CLINICS OF NORTH AMERICA. Nationwide Symposium on The Efficacy of New Drugs. 27 contributors, 217 pages. Philadelphia: W. B. Saunders Co., 1954.

This 1954 number of The Medical Clinics represents a nationwide symposium on the efficacy of new drugs. There are fourteen other clinics on the most important subjects in medicine. As the consulting editor points out, "Careful evaluation of the therapeutic effectiveness of a new agent and cautious detailing of possible toxic side reactions become more and more urgent as the variety and quantity of new agents continue to increase. With present-day rapid and effective means of communication, information concerning new methods or agents is almost immediately available to physician and patient alike."

This new volume has been planned to bring comprehensive information on the effectiveness of certain commonly used new preparations or of certain agents now under investigation. The authors also set down the checks and balances applying to these agents, and their own experiences and opinions in the hope that the practicing physician may have at hand the facilities for an adequate evaluation.

The contributors are all experts in their field. The therapy of certain phases of dermatologic allergy, rheumatoid arthritis, rheumatic disease, hypertension, bacterial endocarditis, the use of the new preparation of mercurial diuretics in congestive heart failure, isonicotinic acid hydrazide compounds in the therapy of pulmonary tuberculosis, the use of ACTH and cortisone in the treatment of bronchial asthma, the anticholingergic drugs in gastrointestinal disease, drug therapy of epilepsy, Parkinson's syndrome, treatment of shock, antabuse in alcoholism, chronic leukemia and many other conditions are presented.

Rh-Hr BLOOD TYPES. Applications in Clinical and Legal Medicine and Anthropology. By Alexander S. Wiener, M.D., F.A.C.P. Senior Serologist to the Office of the Chief Medical Examiner of New York City, Assistant Professor in the Department of Forensic Medicine of the New York University Postgraduate Medical School, Brooklyn, New York. 763 pages. New York: Grune & Stratton, 1954. Price $3.75.

This extensive volume is composed of selected articles on immunohematology which appeared in the literature. There is a preface by the editor, Doctor Wiener, who was associated with the late Dr. Karl Landsteiner, and this is followed by several chapters of compelling historical interest. No one is in a better position to review this subject than Doctor Wiener. The volume actually represents the collected

reprints of the author and reveals the extensive scope of Doctor Wiener's contributions to immunohematology and its practical application.

Chapters consist of fundamental observations, pathogenesis of erythroblastosis fetalis, Rh antibodies, Rh-Hr types and their heredity, nomenclature of the Rh-Hr types, anthropologic aspects, erythroblastosis fetalis and exchange transfusion, the M-N-S blood types, medico-legal applications, A-B-O incompatibility in pregnancy, autoantibodies and disease, blood transfusion, fundamental principles, technique of tests and general considerations.

The author's bibliography, which commences with 1929 and extends to the present time, lists 333 articles on the subject, comprising his original research to date. There is a well-organized subject index, as well as an author's index. The binding and format of the book come up to the usual high standard of the publishers.

THE YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY (1953-1954 YEAR BOOK SERIES). Edited by Marion B. Sulzberger, M.D. and Rudolf L. Baer, M.D. 456 pages, including index. $6.00. Chicago: The Year Book Publishers, Inc., 1954.

This volume contains articles abstracted from journals received from December, 1952 through November, 1953.

The principal divisions of the book are: Endocrine Therapy, Physical Therapy, Other Therapy; Eczematous Dermatitis, Atopic Dermatitis and Urticaria; Allergy; Drug Eruptions; Miscellaneous Dermatoses; Cancers; Fungous Infections; Venereal Diseases and Their Treatment (Exclusive of Gonorrhea), et cetera.

Among the subjects stressed are the use of adrenocortical and other steroid hormones and their effects on the physiologic and pathologic cutaneous processes. Considerable emphasis has also been given to the use of atabrine (mepacrine) and of the safer chloroquine in the treatment of various forms of lupus erythematosus and of light-sensitive dermatoses.

The excellent selections made by the editors of this Year Book offer again a classic index to the outstanding trends in the field of dermatology and syphilology.

—I.W.

BODILY CHANGES IN PAIN, HUNGER, FEAR AND RAGE. By Walter B. Cannon, M.D., S.D., LL.D. George Higginson Professor of Physiology in Harvard University. 404 pages, including index. Boston: Charles T. Branford Co., 1953 (2nd ed.).

This is the second edition to a volume first published in 1915. Since that date, investigations, conducted at the Harvard Physiological Laboratory, dealing with bodily changes occurring in conjunction with pain, hunger, and the major emotions, have been continued concurrently with researches in the same field in other parts of the world—Japan, Russia, England, Algiers, and Argentina. During the course of these investigations, a considerable body of new evidence has accumulated concerning the general thesis "that the bodily changes which attend great excitement are directed towards efficiency in physicial struggle." Certain experiments delimiting that part of the brain which controls emotional expression have led to a fresh approach toward origins of emotional displays and experiences.

The revised chapters in this work include the effect of emotions on digestion, general organization of the visceral nerves involved in emotions, methods of demonstrating adrenal secretion and its nervous control and adrenal secretion involved in emotional stress and pain, increase of blood sugar in pain and great emotion,

improved contraction of fatigued muscle after splanchnic stimulation of the adrenal gland and effects of contraction of fatigued muscle of varying the arterial blood pressure, specific role of adrenin in counteracting effects of fatigue, hastening of coagulation of blood by adrenin and in pain and great emotion, et cetera.

Five new chapters have been added to the present edition: emotional increase of blood corpuscles, emotional derangement of bodily functions, thirst, and two theories of emotion. This latter includes a critical discussion of the James-Lange theory of emotions and a presentation of emotion as a function of the optic thalamus, as suggested by the more recent researches. The final chapter contains an interesting discussion on the alternatives for fighting emotions, the desirability of preserving the martial virtues, and the moral substitutes for warfare.

The book is written in a simple, lucid style that should be comprehensible to the intelligent layman without scientific background. —I.W.

FIFTY YEARS OF MEDICINE. By Lord Horder, G.C.V.O., M.D., F.R.C.P. 70 pages, including index. Price, $2.50. New York: Philosophical Library, Inc., 1954.

This volume represents an expanded version of three Harben lectures, delivered in December 1952, at the Royal Institute of Public Health and Hygiene—The Birth of Scientific Medicine, Medicine Enlarges Its Boundaries, and The Present and the Future.

In these lectures, Lord Harben reviews his experiences in the medical profession. Into this interesting account of what he has seen and what he hopes to see in medical development, he has woven many a telling anecdote and flattering tribute to his co-workers. "He is a medical statesman—a rare type, more's the pity—and he has given us a book of reference which should be laid down for the next generation." —I.W.

EMBOLIA Y THROMBOSIS by Th. Naegeli and P. Matis (In Spanish). (With an introduction by F. Arasa of the Comite de Redaccion.) 162 pages, including bibliography. Folia Clinica Internacional, Barcelona, 1954.

Professor Th. Naegeli, Director of the Surgical Clinic of the University of Tuebingen, and his collaborator, P. Matis, have written an excellent résumé concerning Embolism and Thrombosis. In this monograph they do not limit themselves to reviewing the best world bibliography, but count themselves among those who have dedicated themselves most intensively to the investigation of those themes. Also, they include the investigations and experiences of the famous school of Tuebingen. The theme, as is known, does not belong to this or that specialty, but interests the whole medical world, since Embolism, as well as Thrombosis, is very frequent and common to all branches of medicine. In this monograph one studies in detail all that relates to these complications and, in a very special manner, its treatment. Part I includes morphology and formation of the thrombus, localization and classification of the thrombi, time and frequence of its appearance, pathogenesis of thrombogenesis, and predisposing factors. The second part covers diagnosis of thrombosis and embolism, fundamentals of prophylactic and therapeutic methods, treatment of thrombo-embolism, and prophylaxis of thrombo-embolism. Part III deals with contra-indications and complications of the inhibiting factors of coagulation, and relations of thrombo-embolism with different therapeutic means. The fourth part discusses later sequels of thrombosis and final considerations. The book also contains an appendix and bibliography. —I.W.

Contents for July-August, 1954

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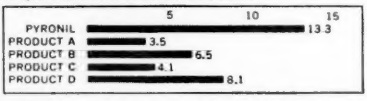

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